Silver(I)-Mediated Decarboxylative Transformations; Benzoic Acids as Aryl Donors in Organic Synthesis

A thesis submitted for the degree of Doctor of Philosophy

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"All that glitters may not be gold. But at least contains free electrons"

-John Desmond Baernal-

"Chemists are a strange class of mortals, impelled by an almost maniacal impulse to seek their pleasures amongst smoke and vapour, soot and flames, poisons and poverty, yet amongst all these evils I seem to live so sweetly that I would rather die than change places with the King of Persia."

-Johann Joachim Becher, 1667-

Als meus pares Josep i Imma

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Declaration

I declare that the work presented in this thesis is my own and that no part of it has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning.

Those parts of this thesis having previously been published in the primary literature at the time of writing:

1. Cornella, J.; Sanchez, C.; Banawa, D. Larrosa, I. Silver-catalysed protodecarboxylation of *ortho*-substituted benzoic acids. *Chem. Commun.* **2009**, *46*, 7176.
2. Cornella, J.; Lu, P., Larrosa, I. Intermolecular decarboxylative direct C3 arylation of indoles with benzoic acids. *Org. Lett.* **2009**, *11*, 5506.
3. Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. Silver-catalyzed protodecarboxylation of heteroaromatic carboxylic acids. *Org. Lett.* **2009**, *11*, 5506.
4. Cornella, J.; Lalhali, H. Larrosa, I. Decarboxylative homocoupling of (hetero)aromatic carboxylic acids. *Chem. Comm.* **2010**, *46*, 8276.
5. Cornella, J.; Rosillo-Lopez, M.; Larrosa, I. A novel mode of reactivity for gold(I): the decarboxylative activation of (hetero)aromatic carboxylic acids. *Adv. Synth. Catal*. **2011**, *353*, 1359.
6. Cornella, J.; Righi, M.; Larrosa, I. Carboxylic acids as traceless groups for formal meta-selective direct arylation. *Angew. Chem. Int. Ed.* **2011**, *50*, 9429.
7. Cornella, J.; Larrosa, I. Decarboxylative C−C bond forming transformations of (hetero)aromatic carboxylic acids (review). *Synthesis* **2012**, 44, 653
8. Grainger, R.; Nikmal, A.; Cornella, J.; Larrosa, I. *Org. Biomol. Chem.* **2012**, *ASAP*, doi: 10.1039/C2OB25157D

Signature……Date……

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Durant el transcurs de la tesi, em preguntava de tant en tant com i què escriuria als agraïments. El que sabia del cert però, era que ho escriuria en català. Perquè penso i sento en català.

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List of abbreviations

Ad	1-Adamantyl
ACN	Acetonitrile
Ar	Aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Biphen	Biphenyl
Bn	Benzyl
BQ	1,4-Benzoquinone
CI	Chemical ionisation
cod	Cyclooctadiene
conc	Concentration
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohexyl
DCE	1,2-Dichloroethane
dcpe	Bis(dicyclohexylphosphino)ethane
DG	Directing group
Diglyme	1-Methoxy-2-(2-methoxyethoxy)ethane
(R,R)-DIOP	(4*R*,5*R*)-(−)-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane
DMA	*N*,*N*-Dimethylacetamide
DMAP	Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dtbpy	2,6-Di-*tert*-butylpyridine
EDG	Electron-donating group
Equiv	Equivalent
ESI	Electro-spray ionisation
EWG	Electron-withdrawing group
Het	Heteroaromatic
HRMS	High resolution mass spectrometry

IMes	1,3-Dimesityl-2,3-dihydro-1*H*-imidazole
IPr	1,3-Bis(2,6-diisopropylphenyl)-2,3-dihydro-1*H*-imidazole
IR	Infrared radiation
L	Ligand
M	Molarity
MS	Molecular sieves
MW	Microwave
m/z	mass-to-charge ratio
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
OTf	Trifluoromethansulfonate
PCy_3	Tricyclohexylphosphine
PEPPSI	**P**yridine-**e**nhanced **p**recatalyst **p**reparation **s**tabilization and **i**nitiation
Phen	Phenanthroline
PivOH	Pivalic acid
Piv	Pivaloyl
ppm	Parts per million
$P(o\text{-tol})_3$	Tris-(*ortho*-tolyl)phosphine
R	Generic substituent
RDG	Removable directing group
rt	Room temperature
SIPr	1,3-Bis(2,6-diisopropylphenyl)imidazolidine
t	Time
T	Temperature
TBAC	*tert*-Butylammonium chloride
TBS	*tert*-Butyldimethylsilane
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetate
TFAA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography

TMS	Tetramethylsilane
TMSO	Tetramethylenesulfoxide
Tol	Tolyl
Ts	Tosyl
TS	Transition state
UV	Ultraviolet radiation

Abstract

The use of aromatic carboxylic acids as coupling agents in cross-coupling reactions has arisen in the past few years as a very useful tool for organic chemists. The generation of CO_2 as the main byproduct has placed this novel approach amongst the greenest alternatives to the traditional cross-couplings, where stoichiometric metal salt waste is usually generated. This thesis contains the study of a novel decarboxylative approach towards the synthesis of C–C bonds for the formation of biaryl structures based on Ag(I) salts. The introduction contains an overview of the recent developments that have appeared in the literature concerning this novel mode of activation, and a discussion on how decarboxylative transformations have given rise to powerful methodologies involving high atom and step economy.

This thesis starts describing the development of the first intermolecular decarboxylative direct arylation protocol. Such methodology was applied to the direct arylation of indoles using benzoic acids as coupling partners. This reaction proceeds in a regioselective fashion giving exclusively the arylated product at the C3 position.

Moreover, the use of catalytic amounts of Ag(I) salts were found to efficiently protodecarboxylate a wide range of benzoic acids bearing electron-withdrawing or electron-donating groups at the *ortho* position. In addition, such protocol was applied to heteroaromatic acids bearing α heteroatoms to the carboxylic acid. (Hetero)aromatic carboxylic acids were also proven to be suitable candidates to perform decarboxylative homocoupling to give good yields of the dimers.

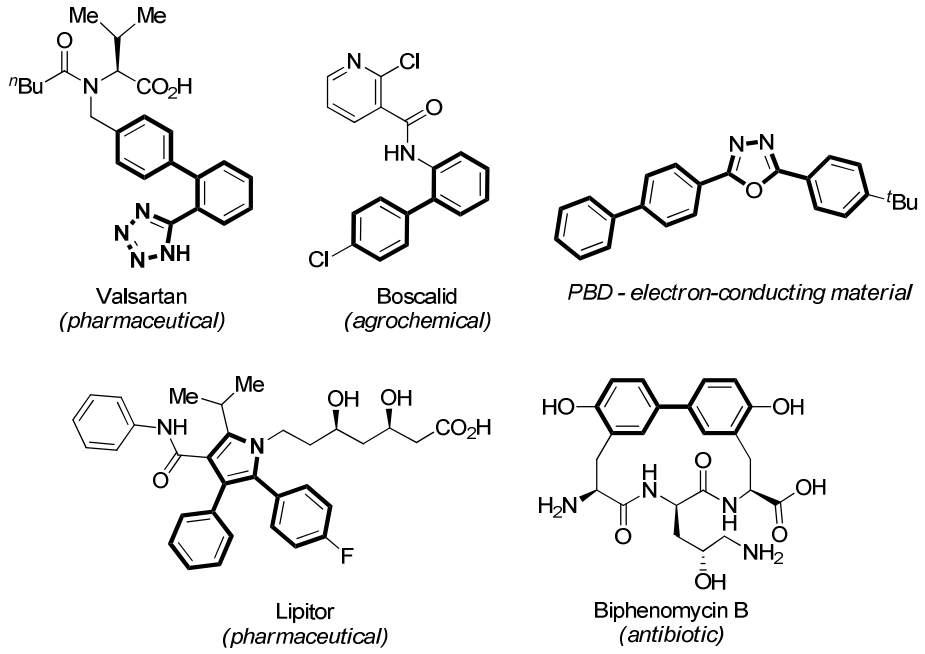
Further to the Ag(I)-mediated decarboxylative methodologies, Au(I) salts were also found to undergo decarboxylation of (hetero)aromatic carboxylic acids providing a wide range of stable aryl-gold(I) compounds with excellent yields.

Finally, the first methodology for a *meta*-selective direct C–H arylation using iodoarenes as coupling partners is also reported. This process, which is compatible with a wide range of *meta* substituents, utilises carboxylic acids as traceless directing groups affording complete control upon the regioselectivity of the direct C–H arylation.

Chapter 1. Decarboxylative C–C bond forming transformations of (hetero)aromatic carboxylic acids

1.1. Introduction

The construction of biaryl structures is of great interest in organic chemistry as these motifs are part of a wide variety of molecules, such as pharmacologically active molecules,[1] natural products[2], agrochemicals[3] and organic materials[4] (Scheme 1).

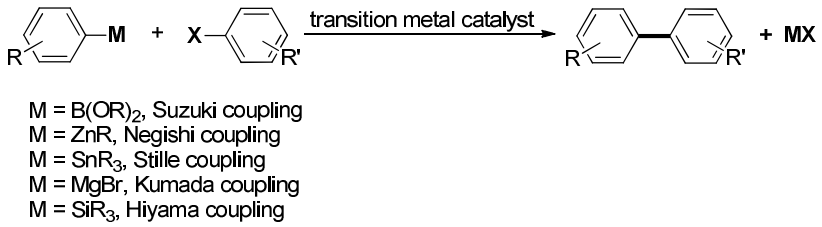


Scheme 1. Examples of biaryl-containing molecules.

For example, Lipitor is a pharmaceutical for the treatment of high cholesterol levels. This drug generated $12.5 billion in 2009 and is amongst the most sold drugs in the world. Valsartan is another pharmaceutical used to reduce blood pressure and is also a worldwide blockbuster drug ($6.0 billion in 2009). Other examples include Boscalid, a crop fungicide, and the organic material PBD.[4] Antibiotics such as biphenomycin B (protein biosynthesis inhibitor) also contain a biaryl structure in its core. These examples highlight the importance of biaryl structures and their synthesis has become an important area of research for synthetic chemists.

An obvious disconnection for the synthesis of biaryls is the aryl−aryl C−C bond. The most widely used method to construct such bonds is the cross-coupling reaction. This chemical process is well utilised in organic chemistry and it occupies a preferential place in general organic chemistry textbooks as well as being the most widely employed C−C bond formation reaction in industry. The importance and impact of this transformation were recognized in 2010, when Akira Suzuki, Richard Heck and Eichi Negishi received the Nobel Prize in Chemistry for their contributions on "*Palladium-catalysed cross-couplings in organic synthesis*".[5]

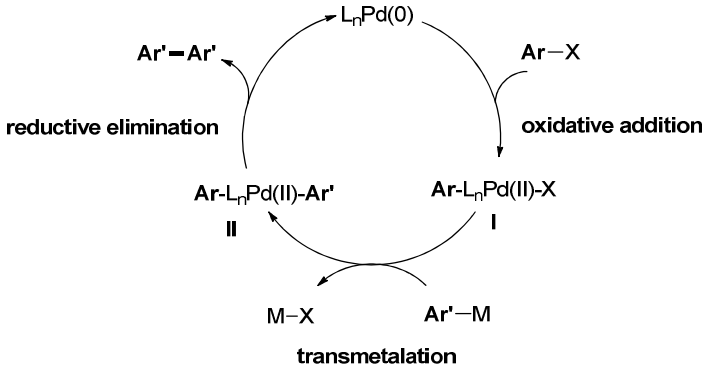
Specifically, this process makes the use of an organometallic reagent which is coupled with a haloarene in the presence of a transition metal catalyst to form a new C−C bond (Scheme 2).



Scheme 2. Traditional cross-coupling transformations.

As depicted in Scheme 2, different metals can be present on the organometallic reagent. Depending on the nature of such metals, the reaction adopts different names, after the chemist who developed each particular cross-coupling.

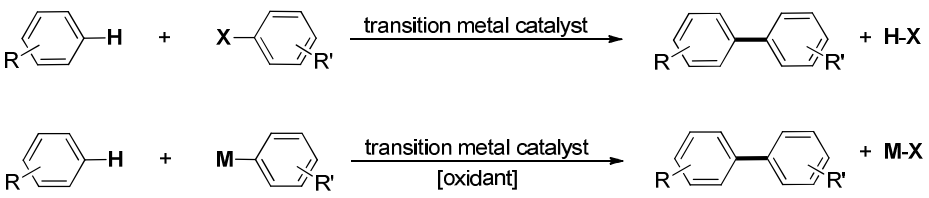
The traditional mechanism for this transformation is very complex and still under debate. However, it is generally agreed that three key steps take place as outlined in Scheme 3. Initially, the haloarene undergoes oxidative addition into the Pd(0) center to form species **I**. Then, **I** transmetalates with a molecule of organometallic reagent to form the bis aryl-Pd(II) species **II** which after reductive elimination would afford the biaryl structure with concomitant formation of Pd(0), which re-enters the catalytic cycle.



Scheme 3. Mechansim of the traditional Pd-catalysed cross-coupling reaction.

However, despite their great efficiency, cross-couplings still present several intrinsic disadvantages namely i) the preparation of the organometallic reagent (Ar'-M), which requires several synthetic steps and ii) the generation of stoichiometric amounts of metallic salts (M-X) derived from the coupling partners.

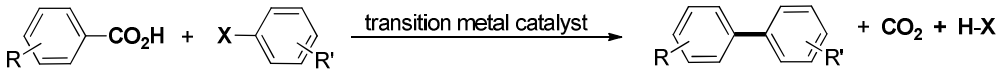
Therefore, since its discovery, intense effort has been placed on developing sustainable and environmentally friendly strategies for the construction of biaryls. Consequently, chemists have focused their attention towards more atom- and step-economic alternatives of the same reaction. As a result, new modes of activation have been developed to fulfill such requirements. In particular, C–H activation based strategies have received much attention since no prefunctionalization of the coupling partner is needed (Scheme 4). In this vein, C–H activation based methodologies could be divided in two main groups: when a simple C−H bond is coupled with a haloarene, thereby avoiding the use of an organometallic reagent; or when the C−H bond is used in place of the haloarene. In the latter, however, an oxidant to reoxidise the catalyst is needed.



Scheme 4. C−H activation based methodologies.

These C–H activation based methodologies, however, still present a general main disadvantage: the control of the regioselectivity. As a result of the large number of C–H bonds present in a molecule, selectively activating one specific position presents a challenge.

Recently, decarboxylative transformations (C–CO_2H activation) have arisen as an excellent alternative to the traditional cross-couplings (Scheme 5).



Scheme 5. Decarboxylative cross-couplings.

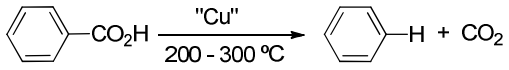
Consequently, such C–C bond activation has captivated chemists' interest due to the ready availability and low cost of common benzoic acids. Unlike C–H activation strategies, decarboxylative activation allows complete control over the regioselectivity of the reaction. In addition, the formation of only CO_2 as the main byproduct places decarboxylative transformations amongst the greenest alternatives to cross-couplings developed to date.

The largest scale cross-coupling in industry is employed for the production of Boscalid (BASF, ca 1000 t/a) (Scheme 1).[3] Therefore, Boscalid is a great example to illustrate the advantages of decarboxylative transformations over traditional cross-couplings. Currently, a Suzuki cross-coupling step is used to generate the biaryl structure, which generates approximately 660 tons of the "$ClB(OH)_2$" byproduct. However, if this step was replaced by a decarboxylative coupling, the industrial production of this compound would only generate 360 tons of innocuous CO_2, which corresponds to the same amount of CO_2 produced by 40 people in one year.[6]

In this chapter, an overview of the fruitful use of aromatic benzoic acids as surrogates for the formation of C–C bonds is presented.

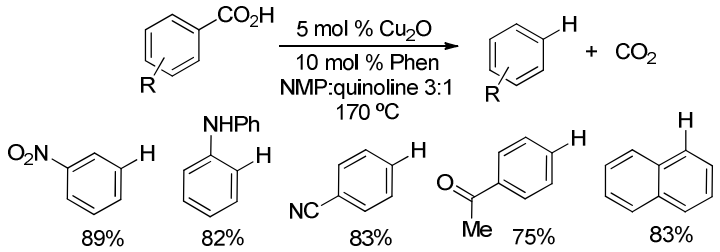
1.2. Decarboxylative activation

Shepard in 1930,[7] and Nilsson,[8] Cohen[9] and Sheppard subsequently,[10] reported that benzoic acids undergo protodecarboxylation in the presence of stoichiometric Cu salts when heated at high temperatures with concomitant formation of CO_2 (Scheme 6).



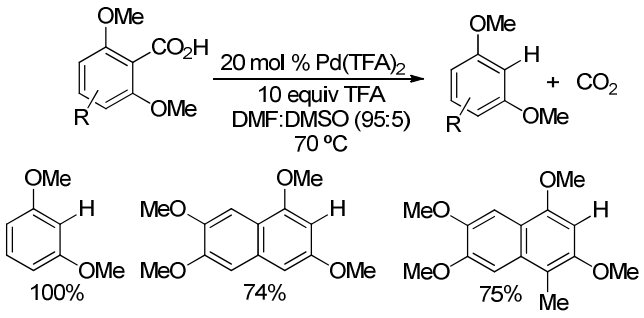
Scheme 6. Decarboxylation of benzoic acids in the presence of Cu salts.

It was not until 2007 that a general methodology for the protodecarboxylation of aromatic carboxylic acids catalytic in Cu was developed.[11] In this work by Goossen *et al.*, the use of a catalytic system based on Cu_2O and 1,10-phenanthroline catalysts in a quinoline:NMP solvent mixture allows for the protodecarboxylation of a wide variety of aromatic carboxylic acids at temperatures of 170 °C. Mechanistic studies suggest the formation of aryl-Cu species as intermediates which upon protonation afford the protodecarboxylated products (Scheme 7).



Scheme 7. Cu(I)-catalysed protodecarboxylation of aromatic carboxylic acids.

Cu is not the only transition metal capable of mediating the decarboxylation process of benzoic acids. In 2005 Myers *et al.* reported mechanistic studies which demonstrated that highly electron-rich trimethoxy substituted benzoic acids are readily decarboxylated at 70 °C with stoichiometric $Pd(TFA)_2$.[12] Subsequently, Kozlowski *et al.* developed a Pd(II)-catalysed protodecarboxylation protocol for a variety of benzoic acids containing two electron-donating groups in both *ortho* positions and in the presence of 10 equiv of a strong acid (Scheme 8).[13]



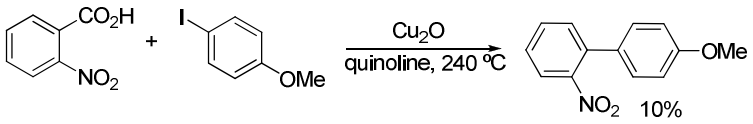
Scheme 8. Pd(II)-catalysed protodecarboxylation of aromatic carboxylic acids.

Despite the limited substrate scope, these decarboxylations proceed at remarkably low temperatures (70 °C). Cole-Hamilton also reported the protodecarboxylation of 4-hydroxybenzoic acid catalysed by Pd salts.[14]

In summary, the last few years have seen advances in the development of new protocols for the decarboxylative activation of aromatic carboxylic acids with different transition metals. However, these protocols suffer from the need for drastic conditions (Cu) or limited substrate scope (Pd). Therefore, novel methodologies which benefit from milder reaction conditions and tolerate a wider range of functionalities are still required. These challenges are addressed in the following chapters of this thesis.

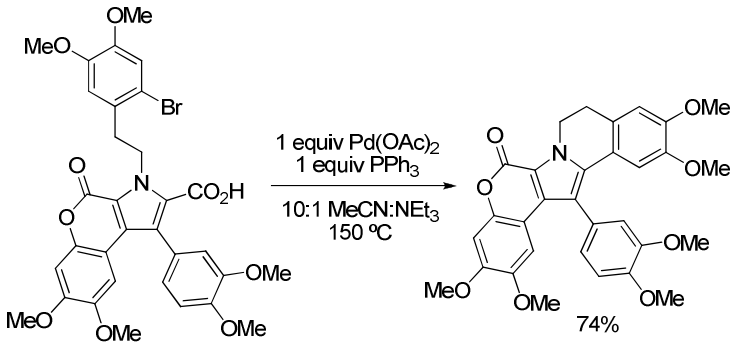
1.3. Decarboxylative cross-coupling reactions

Decarboxylative cross-couplings have received much attention over the past few years as a greener and environmentally friendly alternative to the costly and wasteful traditional cross-couplings. However, this new type of transformation has its origins in a few seminal works, which date back to the 1960‘s. In 1966, in a pioneering work, Nilsson *et al*. observed the formation of biaryls when mixing a benzoic acid with a iodoarene in the presence of stoichiometric amounts of Cu_2O in quinoline at 240 ºC (Scheme 9).[15]



Scheme 9. Cu-mediated decarboxylative arylation of 2-nitrobenzoic acid and *p*-iodoanisole.

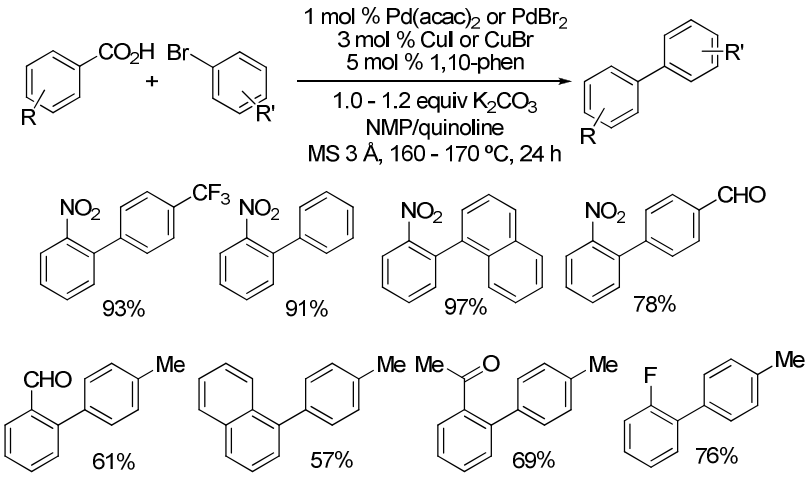
Almost thirty years later, in 1997, Steglich *et al.* reported the first example of an intramolecular decarboxylative arylation.[16] During their work on the biomimetic synthesis of lamellarin G trimethyl ether, Steglich introduced a decarboxylative arylation as the last step of the synthesis (Scheme 10). The use of triethylamine and stoichiometric amounts of $Pd(OAc)_2/PPh_3$ in acetonitrile at 150 ºC allowed the coupling of the pyrrole moiety with the bromophenyl group in 74% yield. In the study, a Heck-type coupling on the pyrrole unit followed by the decarboxylation was suggested as a plausible mechanism.



Scheme 10. Decarboxylative arylation step on the synthesis of lamellarin G.

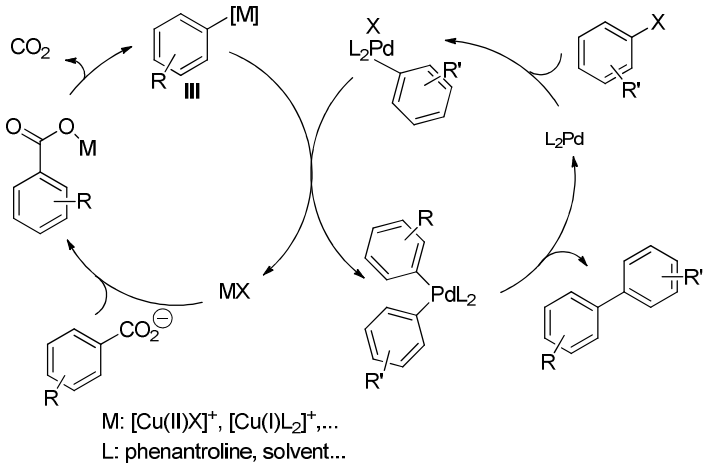
1.3.1. Pd/Cu systems

In 2006, a groundbreaking report from Goossen and co-workers described the first metal-catalysed decarboxylative arylation reaction.[17] Benzoic acids bearing *ortho* substituents could be coupled with aryl bromides in the presence of 1 mol % $Pd(acac)_2$, 3 mol % CuI, 5 mol % 1,10-phenanthroline, 1.2 equiv K_2CO_3, MS 3 Å in a mixture of NMP and quinoline at 160–170 ºC (Scheme 11).



Scheme 11. Pd/Cu-catalyzed decarboxylative coupling of benzoic acids and aryl bromides.

The authors proposed a mechanism based on a double Pd/Cu catalytic cycle (Scheme 12), where a Cu(I) or (II) salt is responsible for mediating the decarboxylation step to the aryl-Cu species **III**. On the other hand, a Pd(0/II) second catalytic cycle mediates the cross-coupling of the arylbromide with the in situ formed aryl-Cu species **III**.

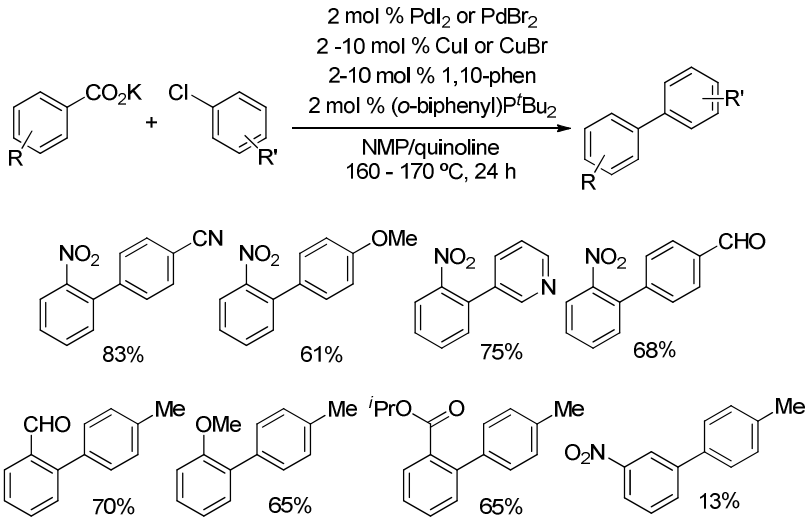


Scheme 12. Proposed mechanism for the Pd/Cu-catalysed decarboxylative synthesis of biaryls.

The authors observed that the addition of halides retards the decarboxylation step. They suggested that the *ortho* substituent in the benzoic acid was necessary in order to displace the halide (X) in the CuX catalyst via coordination in a bidentate fashion. In the absence of the *ortho* substituent in the carboxylic acid, a process catalytic in Cu

is not possible and stoichiometric amounts of $CuCO_3$ and KF are required. This system required lower temperatures (120 °C) which was attributed to the formation of Ar-CO_2-Cu-F species, which seem to lower the decarboxylation barrier.

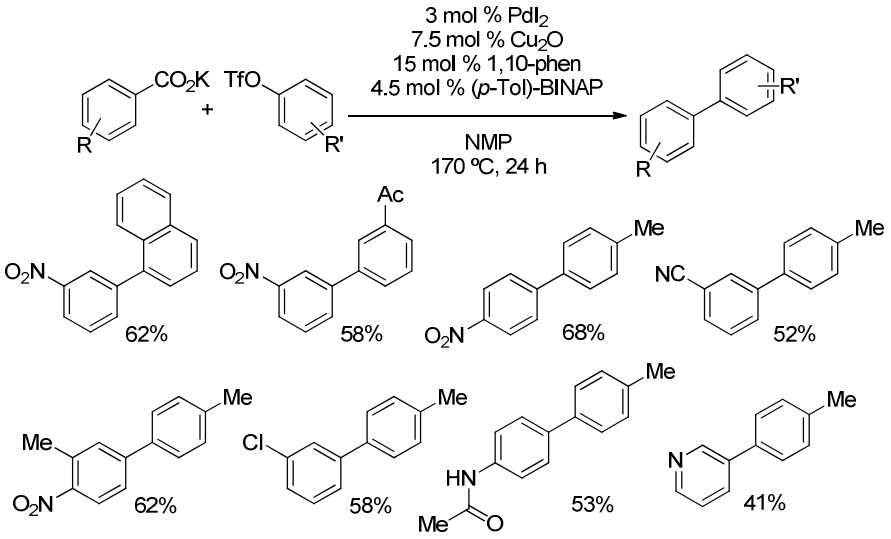
The low cost and greater structural diversity of aryl chlorides prompted the development of a new catalyst system to perform the decarboxylative cross-coupling of benzoic acids with such coupling partners. This was possible with the addition of *ortho*-biphenyl-di-*tert*-butylphosphine ligand for the Pd.[18] Whereas in the previous reports an external base was used, therein the authors reported the coupling with the potassium salt of the benzoic acid. The use of catalytic amounts of PdI_2 or $PdBr_2$, (*o*-biphenyl)P^{t}Bu$_2$, CuI or CuBr, and 1,10-phenanthroline in a NMP/quinoline mixture at 160 ºC allowed excellent yields of the corresponding biaryls (Scheme 13). Similarly to the previous study, when benzoic acids lacking the *ortho* substituent were subjected to the decarboxylative arylation protocol low yields were obtained.



Scheme 13. Pd/Cu-catalysed decarboxylative coupling of aryl chlorides and potassium carboxylates.

The issue of the need for an *ortho* substituent was resolved when a methodology using aryl triflates as coupling partners was reported by the same authors.[19] This method tolerates a wide range of heteroaromatic and benzoic acids in the presence of 7.5 mol % Cu_2O, 15 mol % 1,10-phenanthroline, 3 mol % PdI_2, 4.5 mol % of the sterically demanding (*p*-Tol)-BINAP (2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl) in NMP at 170 ºC (Scheme 14). In this case CuOTf species are generated during the

reaction (as opposed to Cu-halide species). As carboxylates are able to successfully compete against triflates for the coordination sites at the Cu(I) center, the reaction is broadly applicable to aromatic potassium carboxylates regardless of their substitution pattern.



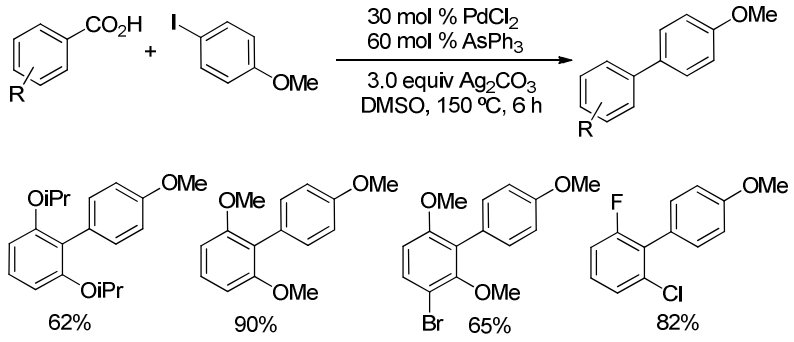
Scheme 14. Pd/Cu-catalyzed decarboxylative coupling of aryl triflates and potassium carboxylates.

Further to the study of aryl triflates, Goossen *et al.* also unveiled that potassium salts of aromatic carboxylic acids could undergo decarboxylative cross-coupling with aryl tosylates. Similarly to the aryl triflates, a wide range of different substituents in the aromatic ring of the acid moiety were tolerated. A similar catalytic system was used with the slight change of the phopshine ligand. In this case the use of XPhos (dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine) was essential for the reaction to proceed.[20]

1.3.2. Pd/Ag systems

In 2007, Becht and Wegner developed the first decarboxylative methodology between benzoic acids and aryl iodides without the need of Cu(I) co-catalysts.[21] The reaction, however, requires very high loading of $PdCl_2$ (30 mol %), and the use of $AsPh_3$ (60 mol %) as the ligand in addition to 3 equiv of Ag_2CO_3 (Scheme 15). This process

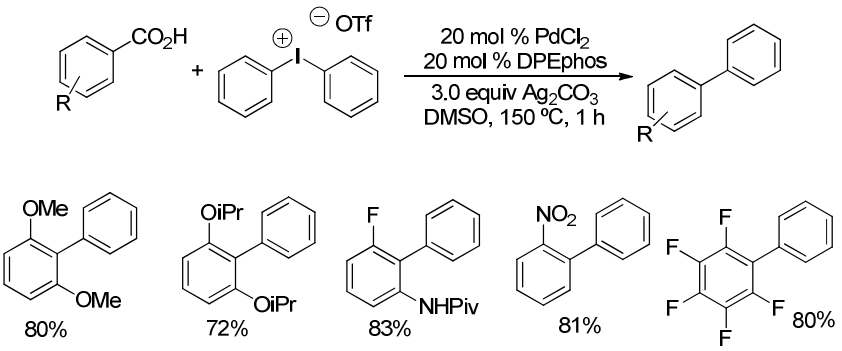
allows coupling between mainly *ortho*-substituted benzoic acids (electron-donating and electron-withdrawing groups) and a variety of aryl iodides.



Scheme 15. Pd/Ag-mediated decarboxylative coupling of aryl iodides and benzoic acids.

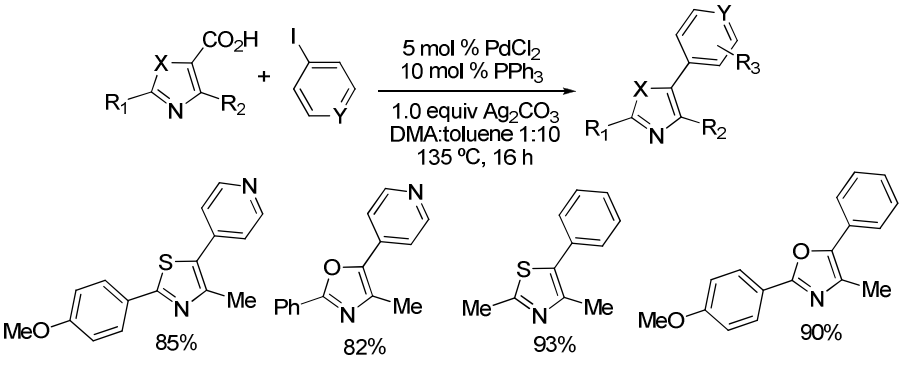
In this report, the authors suggest that the role of Ag_2CO_3 is as a base in the reaction. However, the formation of AgI upon extraction from the PdArI species generated after oxidative addition onto the Pd(0) center could not be ruled out. Consequently, Ag_2CO_3 may be playing several roles in this reaction. Subsequently, Wu *et al.* also disclosed a similar protocol. With the use of lower catalyst loadings (10 mol % of $PdCl_2$) in combination with biphosphine BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) ligand. [22]

Similarly to their first report, Becht and Wegner also disclosed the decarboxylative coupling of *ortho*-substituted benzoic acids with bis-aryl iodonium(III) species (Scheme 16).[23] 20 mol% $PdCl_2$ and 20 mol% of the bidentate phosphine DPEphos ((oxybis(2,1-phenylene))-bis(diphenylphosphine)) were necessary in this case in order to afford good yields of the coupled product.



Scheme 16. Decarboxylative coupling using bis-aryl iodonium species as coupling partners.

In the same line, Greaney and co-workers developed a decarboxylative arylation coupling of heteroaromatic carboxylic acids with aryl iodides and bromides.[24] The coupling with heteroaromatic carboxylic acids required a much lower loading of catalyst (5 mol % $PdCl_2$, 10 mol % PPh_3) in addition to only 1 equiv of Ag_2CO_3. In this work, several aryl iodides and bromides were successfully coupled with 1,3-thiazole-4-carboxylic acid and 1,3-oxazole-4-carboxylic acid (Scheme 17).

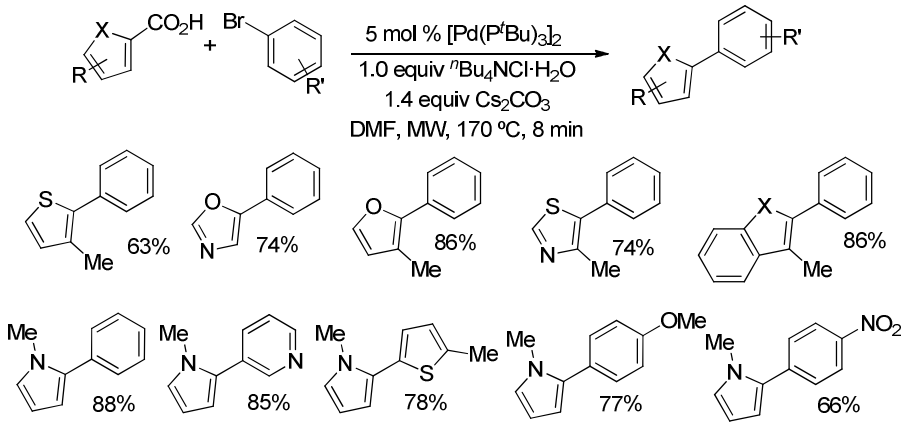


Scheme 17. Decarboxylative coupling of heteroaromatic carboxylic acids with aryl iodides.

It is noteworthy that in most of the studies mentioned in this section, the mechanisms for these transformations are rarely discussed. In addition, the Ag(I) salts used in these methodologies are generally regarded as additives or bases for the reaction. Nonetheless, in any of these examples a possible role for Ag(I) in the decarboxylation step is suggested.

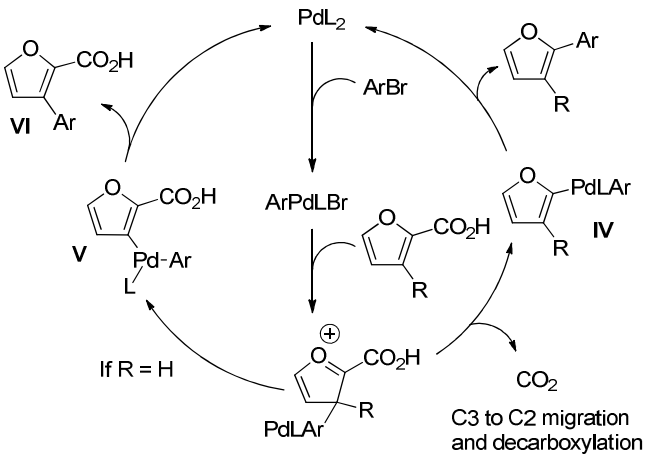
1.3.3. Pd cross-couplings

As mentioned in the introduction, Steglich *et al.*, reported a first approach to decarboxylative cross-couplings using stoichiometric amounts of $Pd(OAc)_2$.[16] This pioneering work was expanded by Forgione and Bilodeau who, in 2006, reported the first Pd-catalysed decarboxylative cross-coupling between heteroaromatic acids and aryl bromides.[25] The reaction proceeds with 5 mol % [$Pd(P^tBu_3)_2$] conjointly with TBAC ($^nBu_4NH^+Cl^- \cdot H_2O$) and Cs_2CO_3 in DMF at 170 ºC using MW heating. The carboxylic acid must be α to the heteroatom for the reaction to proceed (Scheme 18).



Scheme 18. Pd-catalysed decarboxylative arylation of heteroaromatic acids with bromoarenes.

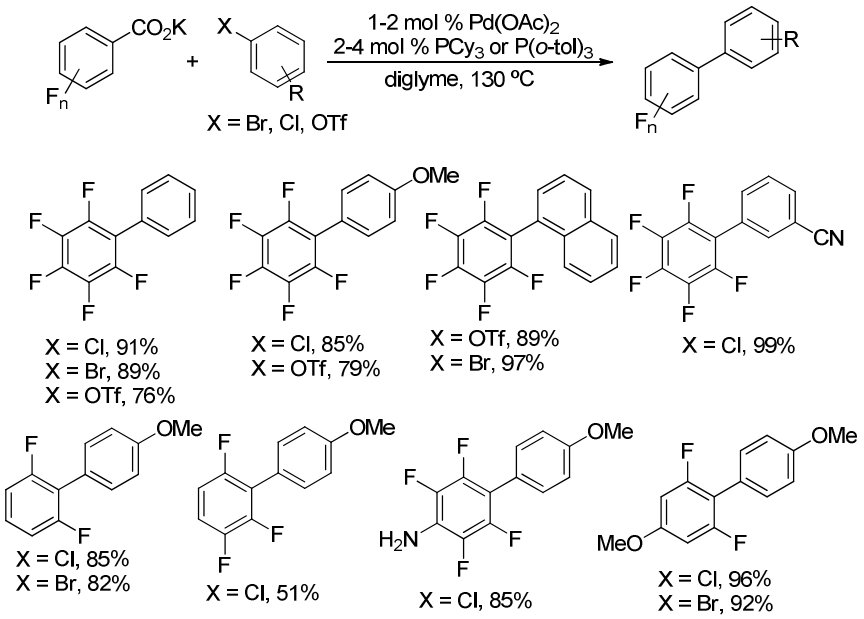
Interestingly, when coupling 2-furancarboxylic acid with bromobenzene the authors observed the formation of small amounts of 2,3-diphenylfuran. In light of this observation, the authors proposed that the PdArBr species formed after oxidative addition undergo electrophilic addition at the C3 position of the furan (Scheme 19). At this stage, two pathways were proposed. If the R substituent is not hydrogen, a C3-C2 migration followed by extrusion of CO_2 produces intermediate **IV** which, after reductive elimination, yields the 2-arylated furan product. On the other hand, if R is hydrogen, deprotonation will lead to intermediate **V**. Reductive elimination of **V** leads to the formation of the C3 arylated furancarboxylic acid **VI**, which can re-enter the cycle delivering the observed C2-C3 arylated byproduct.



Scheme 19. Proposed mechanism for the decarboxylative arylation of heteroaromatic carboxylic acids.

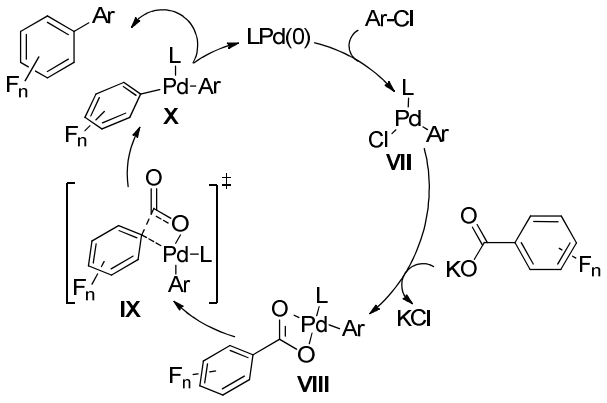
Further to this study, Forgione and Bilodeau expanded this methodology to the coupling of *N*-methyl-pyrrole-2-carboxylic acids with aryl chlorides, iodides and aryl triflates, without the need of modifying the reaction conditions.[26]

In 2010, Liu *et al.* disclosed the Pd-catalysed decarboxylative cross-coupling of polyfluorinated potassium benzoates with a wide range of coupling partners.[27] The presence of $Pd(OAc)_2/PCy_3$ or $Pd(OAc)_2/P(o\text{-tolyl})_3$ catalytic system in diglyme permits a successful coupling with aryl bromides, chlorides and aryl triflates (Scheme 20).



Scheme 20. Pd-catalysed decarboxylative arylation of fluorinated arenes with aryl chlorides, bromides and triflates.

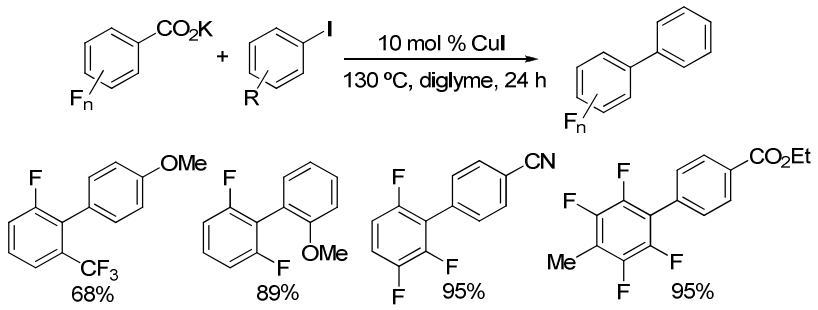
In this report, Liu proposes a mechanism for the decarboxylative transformation with aryl chlorides based on computational studies (Scheme 21). The postulated mechanism starts with an oxidative addition, generating aryl-Pd(II) species **VII**. Subsequently, **VII** forms the aryl-Pd(II) carboxylate **VIII** with the benzoic acid, leading to intermediate **X** via transition state **IX**. The authors postulate a concerted four-member ring transition state for the decarboxylation step being the highest energy point on the reaction profile and therefore the rate-limiting step in the reaction.



Scheme 21. Proposed mechanism for the decarboxylative arylation of perfluorobenzoic acids.

1.3.4. Cu systems

In 2009, Liu *et al.* developed the first synthetically relevant Ullman-type decarboxylative arylation using exclusively Cu(I) as the catalyst.[28] The authors disclosed the cross-coupling of a wide range of polyfluorinated aromatic carboxylates with aryl iodides without the need of a Pd catalyst (Scheme 22). The arylation of aryl bromides is also reported in the same study, although a higher catalyst loading and the use of a ligand are required (20 mol% of CuI/phenanthroline).



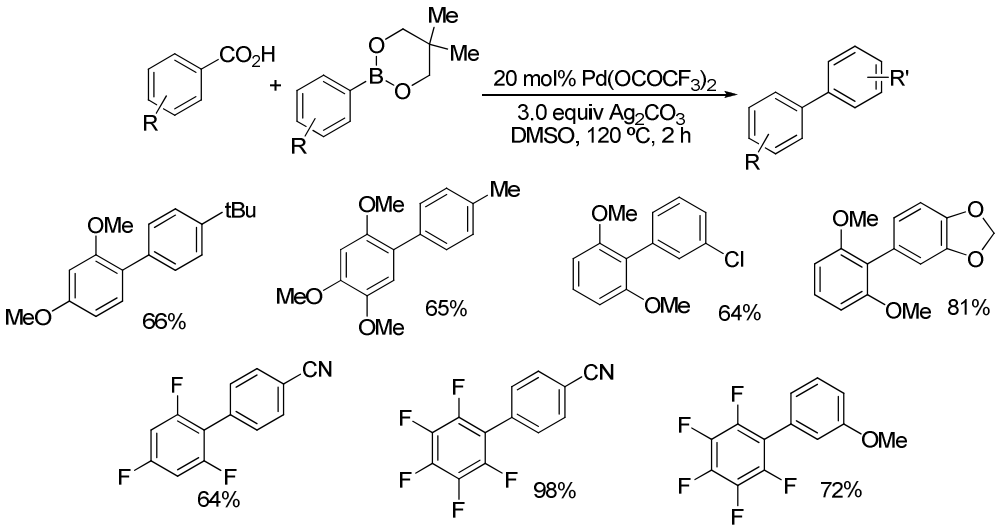
Scheme 22. Cu-catalysed decarboxylative coupling of perfluorobenzoic acids with aryl iodides.

1.4. Oxidative decarboxylative cross-coupling

In all the aforementioned reports, the benzoic acid substrate can be perceived as a replacement for the organometallic reagent in a 'traditional' cross-coupling, and thus, behaving as a nucleophile, while the second coupling partner (a (pseudo)haloarene) plays the role of an electrophile. However, the possibility of coupling two nucleophiles under oxidative conditions could also be contemplated.[29] In this sense, several methodologies have arisen over the past few years where benzoic acids are coupled with aryl boronic esters, alkenes, alkynes and even arenes via C–H bonds functionalisation. In this section, a selection of decarboxylative oxidative protocols is summarised.

1.4.1. Decarboxylative Suzuki cross-coupling

In 2011, Liu *et al.* disclosed the first coupling between aromatic carboxylic acids and boronic esters.[30] The protocol is compatible with a variety of substituents on the aryl boronic ester coupling partner, although the benzoic acid moiety is limited to *ortho*-methoxy benzoic acids and polyfluorinated carboxylic acids (Scheme 23). 3 equiv of Ag_2CO_3 are required for the reaction to proceed, one of which is consumed in reoxidising Pd(0) to Pd(II) in the catalytic cycle.

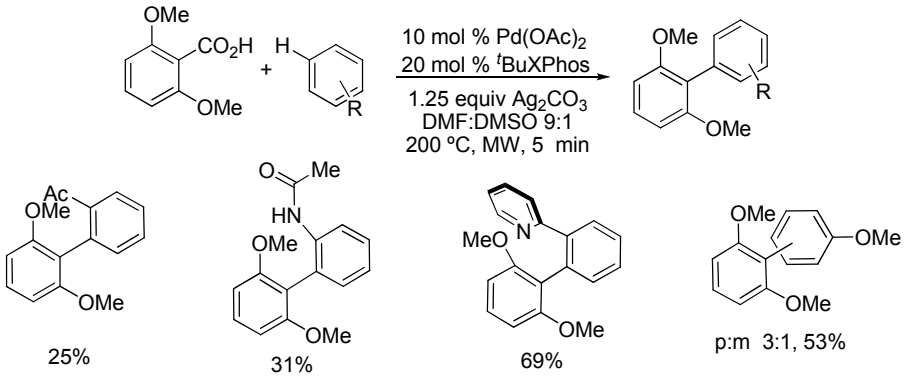


Scheme 23. Decarboxylative arylation with boronic esters.

1.4.2. Decarboxylative C–H arylation

The progression towards atom- and step-economic chemistry has encouraged organic chemists to develop novel methodologies over the years. Hence, for the formation of unsymmetrical biaryls, the combination of two different 'greener' activation methods can be envisaged. In this context, C–H activation could be considered the optimum activation partner to use in combination with C–CO_2H activation. The advantages of this combination include i) minimisation of halogenated and metal waste, ii) no need for prefunctionalisation of any of the coupling partners iii) the use of oxygen as the terminal oxidant would generate H_2O and CO_2 as the only byproducts. Indeed, the combination of these two modes of activation has been reported in the last few years and has given rise to an abundance of different synthetic applications.

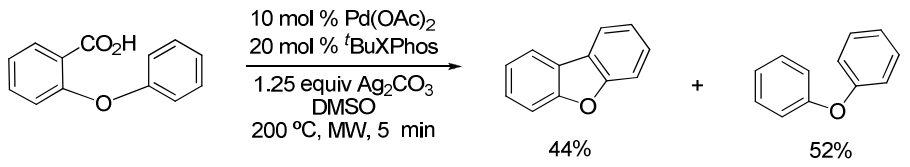
In 2008, Crabtree reported the first approach to a decarboxylative C–H arylation protocol.[31] In this work, the authors successfully reacted 2,6-dimethoxybenzoic acid with four different arenes bearing a directing group. The reaction proceeds using 10 mol % $Pd(OAc)_2$, 20 mol % ^{t}BuXPhos (2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl) and Ag_2CO_3 in DMF:DMSO (Scheme 24).



Scheme 24. Decarboxylative direct C–H arylation of benzoic acids.

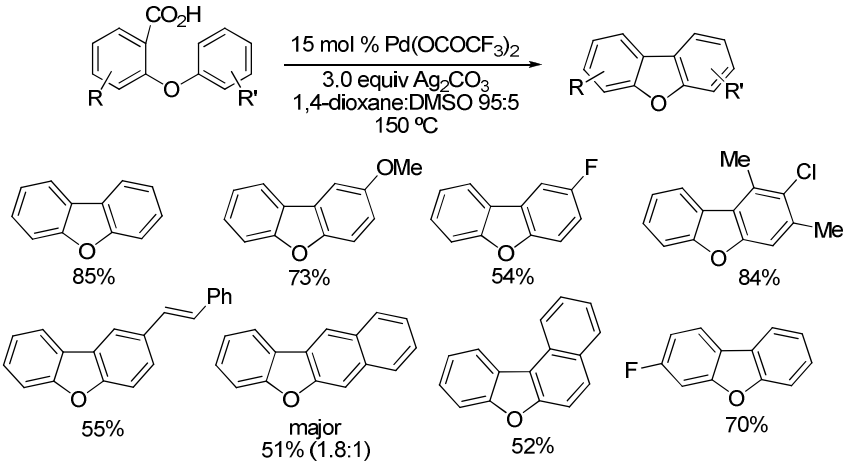
The authors pointed out that the main disadvantage of this transformation stems from the protodecarboxylation of the benzoic acid, leading to the formation of large quantities of 1,3-dimethoxybenzene. Although low yields were obtained over a relatively narrow substrate scope, this methodology illustrates the possibility of combining two of the greenest modes of activation towards cross-couplings.

In this report, the authors also describe an example of an intramolecular decarboxylative arylation using 2-phenoxybenzoic acid. However,, the protodecarboxylated product also appeared to be the main byproduct (Scheme 25).



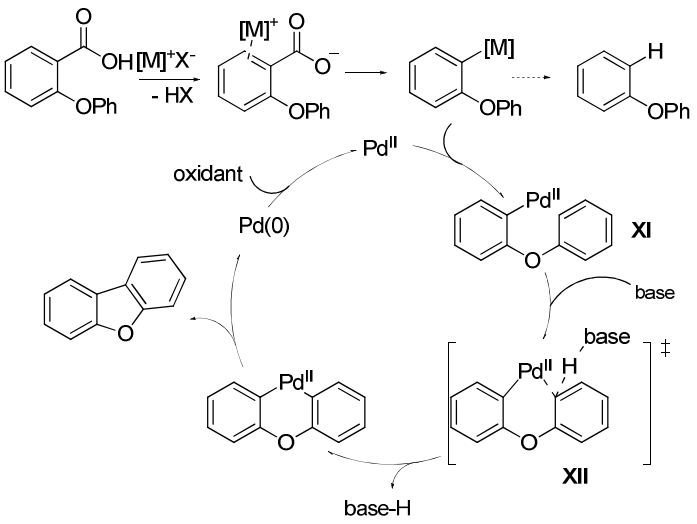
Scheme 25. Intermolecular decarboxylative C–H arylation of benzoic acids.

Glorius *et al.* subsequently reported a more general intramolecular decarboxylative C–H arylation for 2-phenoxy benzoic acids (Scheme 26).[32] The reaction however requires high loading of $Pd(TFA)_2$ (15 mol %) in combination with 3 equiv of Ag_2CO_3 to afford good to excellent yields of the dibenzofurans. Unlike Crabtree's methodology, this method dramatically reduces the protodecarboxylation byproduct down to 1:24 ratio in comparison to the product, presumably through the use of 1,4-dioxane as a co-solvent.



Scheme 26. Intermolecular decarboxylative C–H arylation of benzoic acids.

The authors stated that either the Pd(II) or the Ag(I) could be responsible for the decarboxylation step in this transformation (Scheme 27). After formation of aryl-Pd species **XI**, C–H activation (via transition state **XII**) and reductive elimination would provide the cyclised product. As in the previous examples, Ag(I) reoxidises the Pd(0) back to Pd(II) to close the cycle.



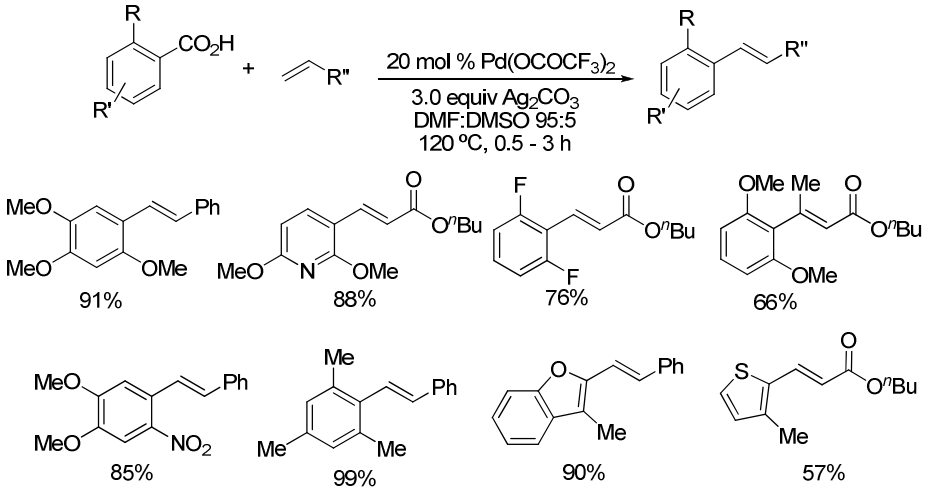
Scheme 27. Proposed mechanism for the intermolecular decarboxylative C–H arylation of benzoic acids.

The initial work of this thesis involves the development of a general intermolecular decarboxylative transformation for the direct arylation of indoles with benzoic acids as coupling partners. Despite neither of these precedents being reported at the start of our work, our methodology avoids the requirement of the extremely high temperatures. This study will be the subject of chapter 2.

1.4.3. Reactions with alkenes

The concept of decarboxylative activation has successfully been extended to the coupling of aromatic carboxylic acids and double bonds. In this section, a selection of the most significant examples of this decarboxylative (and oxidative) Heck-type coupling is reported.

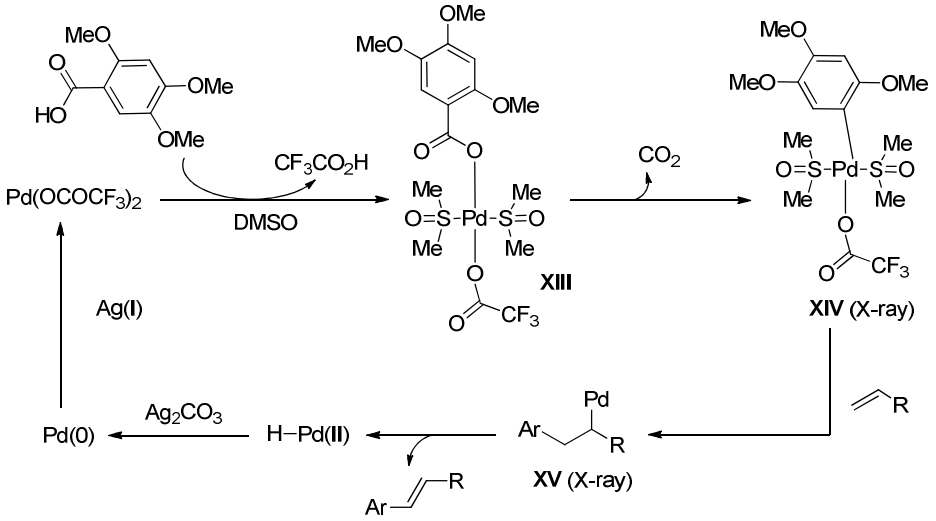
In 2002, a groundbreaking report from Myers *et al*. showed the possibility of coupling aromatic benzoic acids with acrylates and styrenes.[33] This work was the very first example of a decarboxylative Heck-type coupling reported in the literature. The coupling was possible by using $Pd(TFA)_2$ as the catalyst in addition to 3 equiv of Ag_2CO_3. A combination of DMF and DMSO in 95:5 ratio was found to be crucial for the decarboxylative coupling (Scheme 28).



Scheme 28. Decarboxylative Heck-coupling with acrylates and styrene derivates.

A large range of substituted aromatic carboxylic acids was tolerated in Myers' reaction conditions although an *ortho*-substituent was essential. This substituent could be an electron-donating or -withdrawing group or even neutral groups. Furthermore, heteroaromatic carboxylic acids were also found compatible with this protocol.

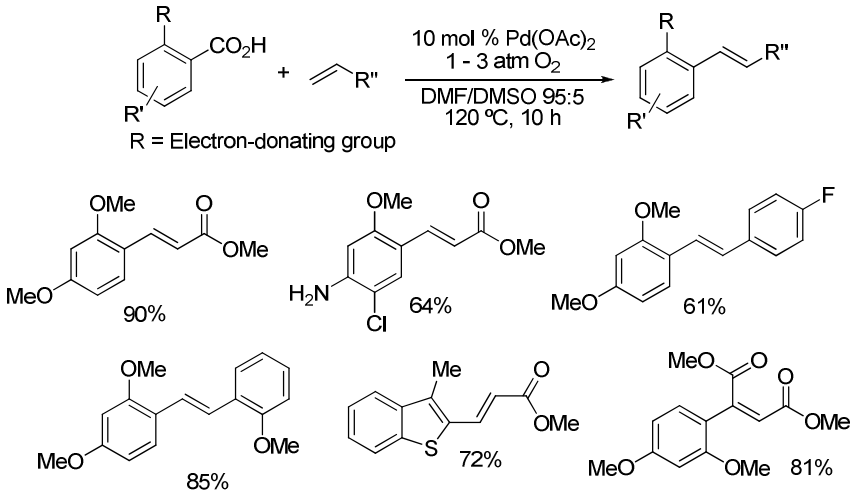
Subsequently, Myers *et al*. turned their attention to the mechanism for the decarboxylative olefination. The authors reported an exhaustive study on the mechanism of the coupling between 2,4,5-trimethoxybenzoic acid and different olefin derivatives.[12] The proposed mechanism, based on kinetic studies together with crystal structures, is depicted in Scheme 29. The authors showed that upon mixing equimolar amounts of $Pd(TFA)_2$ and 2,4,5-trimethoxybenzoic acid in DMSO, the Pd(II) center underwent ligand exchange with the more electron-donating benzoic acid to form the Pd species **XIII**. After monitoring the progress by NMR, this complex quantitatively formed the aryl-Pd(II) species **XIV** with concomitant release of CO_2, demonstrating the Pd(II) is responsible for the decarboxylation step. When the olefin partner was then added to species **XIV**, the formation of the aryl-Pd(II) species **XV** were detected (when norbornene is used, a stable complex is formed and X-ray structures were provided). The authors then stated that β-hydride elimination followed by oxidation of the Pd(0) to Pd(II) by the Ag(I) completes the catalytic cycle.



Scheme 29. Proposed mechanism for the decarboxylative Heck-coupling.

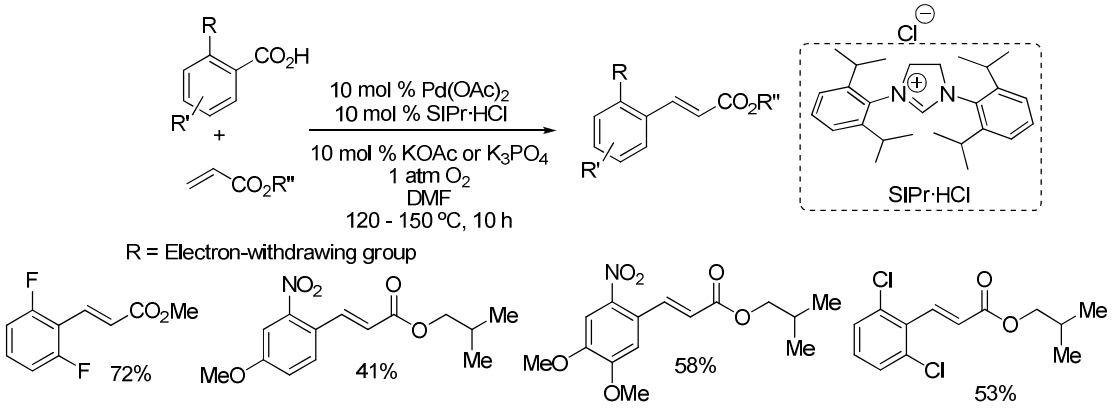
In summary, Myers *et al.* satisfactorily proved that $Pd(TFA)_2$ catalyses the decarboxylation of an electron-donating benzoic acid. However, no comments were made on the possible roles of the Ag(I) salts present in this system.

Later, Su *et al.* expanded the work of Myers and developed a catalyst system where O_2 is used as the oxidant.[34] This remarkable achievement represents the ideal case in terms of atom economy for decarboxylative transformations, as only H_2O and CO_2 will be generated as byproducts. The geometry of the double bond in all cases was >20:1 (Scheme 30).



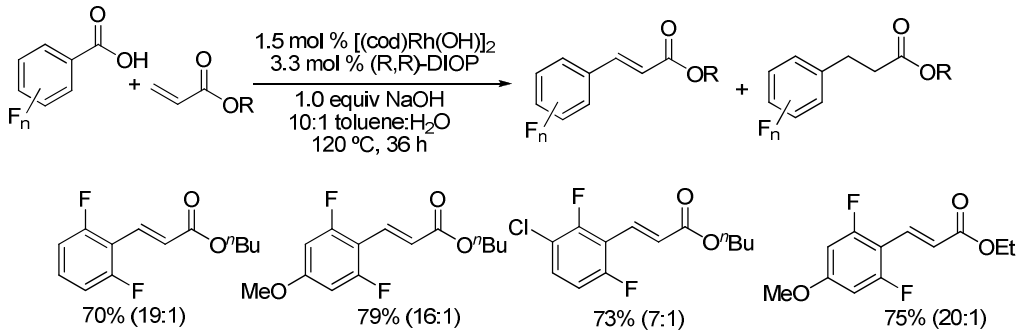
Scheme 30. Decarboxylative Heck-coupling of electron-donating benzoic acids using O_2 as oxidant.

Interestingly, the authors suggest that the use of very electron-rich ligands for the Pd center would facilitate the decarboxylation of electron-deficient acids. Consequently, the use of a strong electron-donor ligand such as the *N*-heterocyclic carbene SIPr was envisaged. Therein, four examples of the coupling were presented thereby allowing the coupling with alkyl acrylates (Scheme 31).



Scheme 31. Decarboxylative Heck-coupling of electron-deficient benzoic acids with O_2 as oxidant.

Whereas Cu, Pd or Ag are involved in all decarboxylative protocols described hitherto, Zhao *et al*. showed that Rh(I) was also capable to undergo decarboxylative activation of benzoic acids; the authors disclosed the first Rh(I)-catalysed decarboxylative Heck reaction.[35] In this work, several examples of fluorinated benzoic acids, which satisfactorily react with alkyl acrylates, are reported. However, the conjugate addition adducts and the protodecarboxylation byproducts are also observed (Scheme 32).

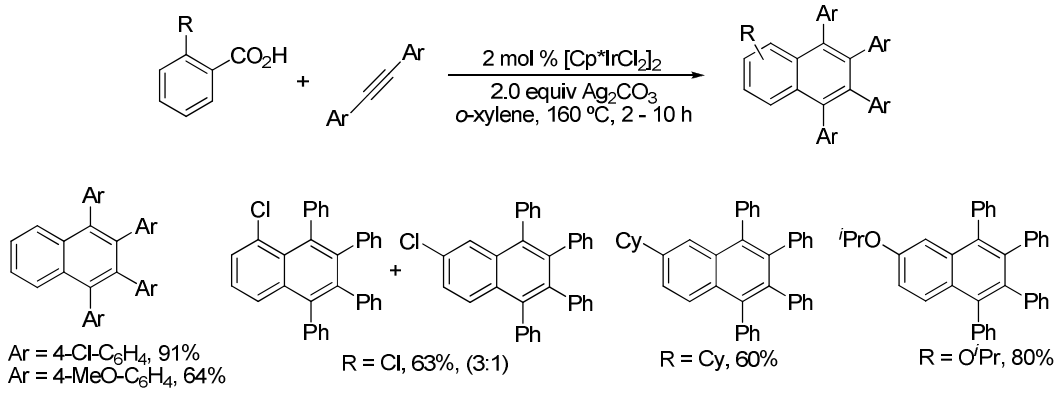


Scheme 32. Rh-catalysed decarboxylative Heck-coupling.

1.4.4. Reactions with alkynes

The use of alkynes as building blocks for C–C bond formation with aromatic compounds through cross-coupling or transition-metal catalysed cycloadditions is well known. In this vein, several research groups have envisaged the use of benzoic acids and therefore, decarboxylative methodologies for the construction of polyaromatic compounds using triple bonds as coupling partners. This section summarises the most relevant work developed in this area.

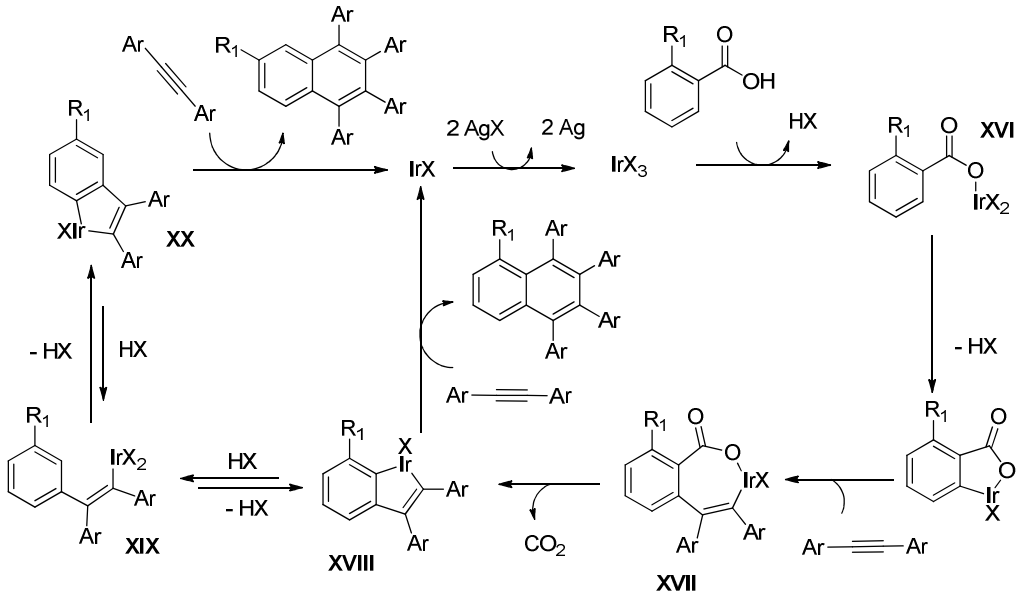
In 2007, Miura and Satoh *et al*. reported the first example of a decarboxylative coupling between benzoic acids and alkynes to form substituted naphthalenes.[36] The main feature of this reaction compared to the previously mentioned cross-couplings is that it proceeds under Ir catalysis. In the presence of $[Cp^*IrCl_2]_2$ (2 mol %) and 2.0 equiv of Ag_2CO_3, a wide range of different naphthalenes were coupled (Scheme 33).



Scheme 33. Ir-catalysed decarboxylative synthesis of naphthalenes.

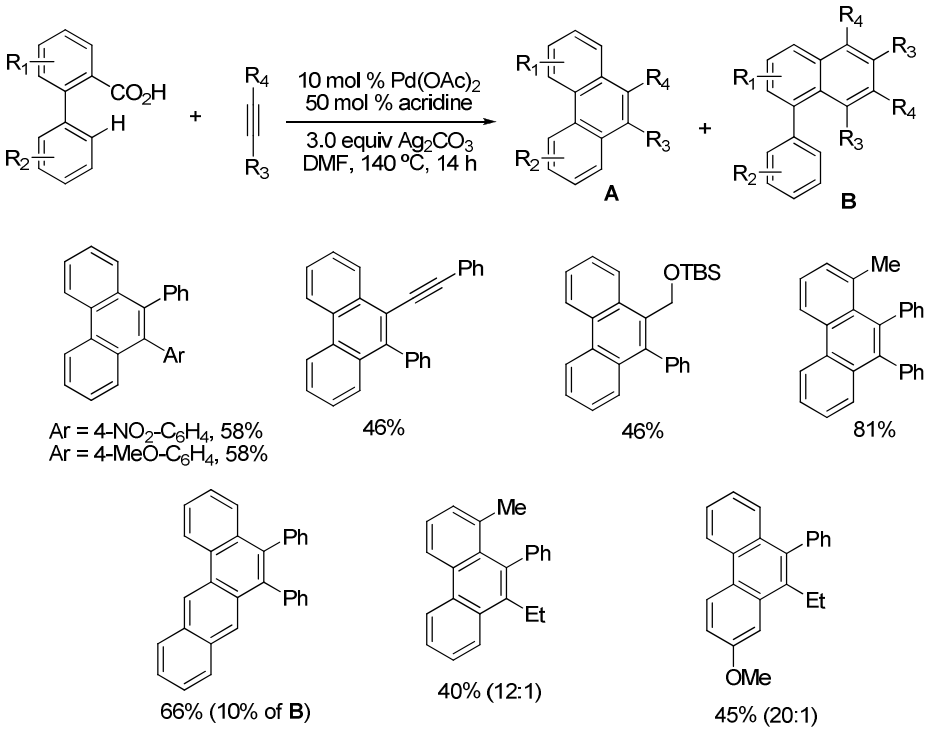
It is worth noting that when the benzoic acid is *ortho*-substituted with Cy or ^{i}PrO a single regioisomer is obtained, whereas when this substitutent is a Cl, a 3:1 mixture of two regioisomers is formed. A proposed mechanism is outlined in Scheme 34. At the onset, the Ir(III) catalyst reacts with the benzoic acid generating Ir-carboxylate **XVI**. Then, C–H activation at the *ortho* position followed by alkyne insertion generates a 7-member ring Ir complex (**XVII**). Subsequent, decarboxylation followed by a second

alkyne insertion and final reductive elimination forms the desired product. Oxidation of Ir(I) to Ir(III) by the Ag(I) salts regenerates the catalyst. The authors suggest that in the case of 2-substituted benzoic acids, iridacycle **XVIII** may undergo rearrangement driven by steric factors through protonolysis to form open intermediate **XIX**. A second C–H activation to form the isomeric iridacycle **XX** followed by a second alkyne insertion delivers the observed naphthalene isomer.



Scheme 34. Proposed mechanisms for the Ir-catalysed decarboxylative synthesis of naphthalenes.

The formation of phenanthrenes via decarboxylative cross-coupling was disclosed by Glorius *et al*. in 2010.[37] A formal [4+2] annulation between 2-phenoxybenzoic acids and alkynes was reported to proceed in the presence of $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (3.0 equiv). A thorough screening of pyridine ligands for the Pd identified acridine as the optimal one (Scheme 35).



Scheme 35. Decarboxylative synthesis of phenanthrenes with alkynes.

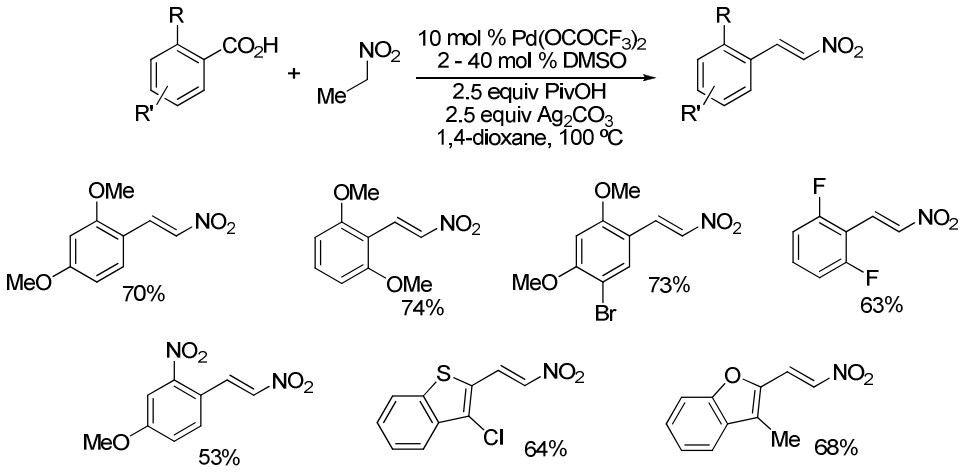
Remarkable regioselectivities (up to 20:1) were obtained when asymmetric alkynes were coupled with phenoxyacids. In addition, it is noteworthy that byproduct **B** is produced in some cases yet in minor quantities. **B** would derive from a decarboxylative double alkyne insertion onto the aromatic ring of the benzoic acid.

1.4.5. Miscellaneous decarboxylative transformations

The application of the decarboxylative activation concept to the formation of C–C bonds beyond the scope of traditional cross-coupling type reactions was also envisaged by several research groups. Consequently, novel transformations were unveiled expanding the possibilities of this mode of activation to different areas. In this section, a few examples of these methodologies are reported.

The coupling between aromatic carboxylic acids and nitroethane was disclosed by Su *et al.*[38] This protocol consists in a combination of cross-coupling/dehydrogenation reaction to afford exclusively (*E*)-β-nitrostyrenes (Scheme 36). The use of $Pd(TFA)_2$

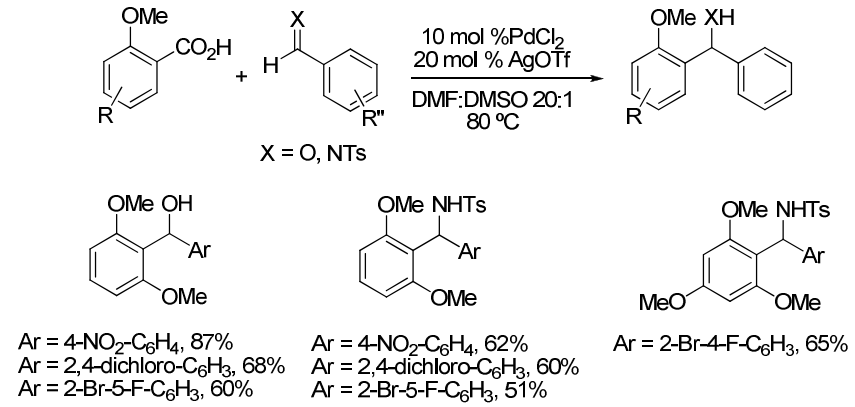
(10 mol %) in combination with Ag_2CO_3 and PivOH (2.5 equiv) permitted the reaction of a wide variety of *ortho*-substituted benzoic acids as well as heteroaromatic carboxylic acids. Su and co-workers showed that the amount of DMSO (which is acting as a ligand for the Pd catalyst) needs to be adapted to each substrate in order to obtain good yields.



Scheme 36. Decarboxylative coupling with nitromethane.

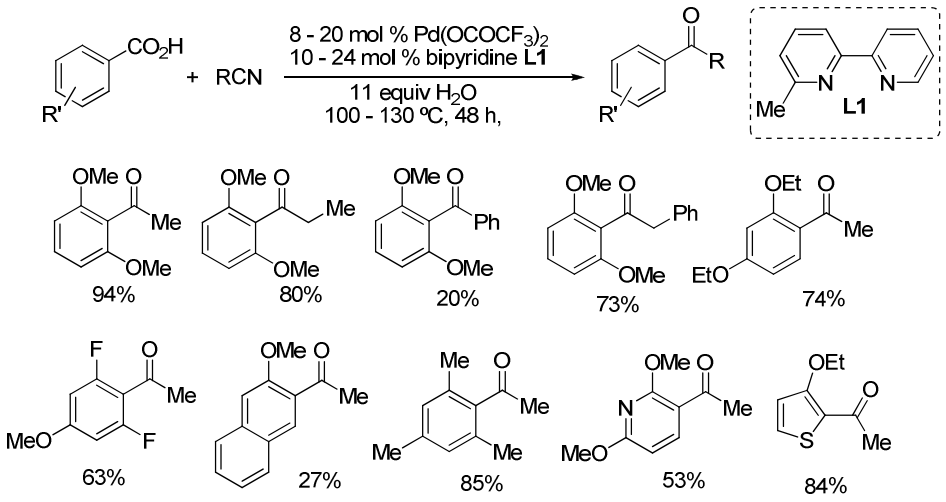
To explain the observed reactivity of nitroethane, and consequently the generation of vinylation products, the authors suggested the formation in situ of nitroethylene followed by a Heck-type coupling. However, the mechanism of this reaction still remains unclear.

Wu and co-workers disclosed the 1,2-addition of benzoic acids to aromatic aldehydes or imines.[39] In this work, the aromatic acid plays the role of aryl donor to form diarylmethyl amines or diarylmethanols (Scheme 37). The reaction proceeds with 10 mol % $PdCl_2$ and catalytic amounts of AgOTf at mild temperatures (80 ºC). Despite the wide variety of aldehydes and imines compatible with these conditions, the protocol is still limited to 2,6-dimethoxybenzoic acids.



Scheme 37. Decarboxylative addition of benzoic acids to aldehydes and imines.

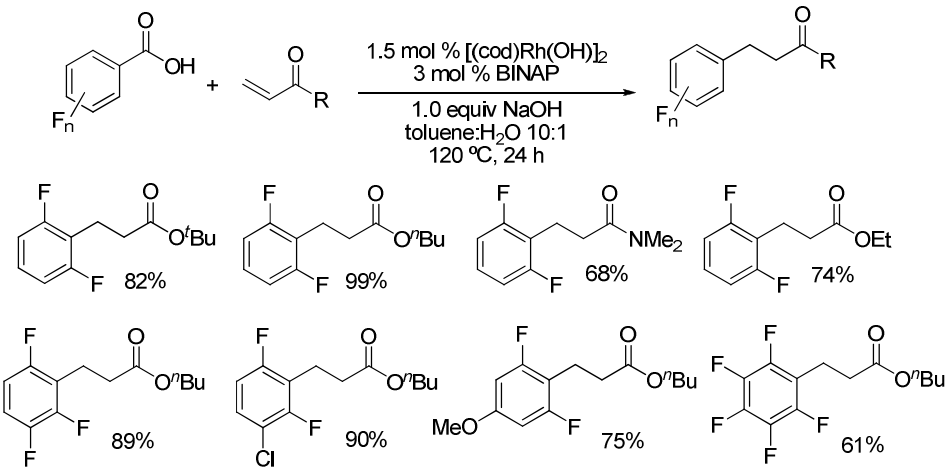
Another C–C bond formation procedure via decarboxylative activation was envisaged by Larhed *et al.*[40] The work describes the synthesis of aryl ketones by decarboxylative addition of benzoic acids to nitriles. This reaction proceeds with the use of catalytic amounts of $Pd(TFA)_2$ in combination with 6-methyl-2,2'-bypiridine (**L1**) as a ligand (Scheme 38). In situ hydrolysis converts the imine product into the corresponding ketone.



Scheme 38. Decarboxylative coupling of benzoic acids and nitriles for the synthesis of ketones.

In another context, Zhao *et al.* developed a protocol for the decarboxylative 1,4-conjugate addition of polyfluorinated benzoic acids to Michael acceptors. Unlike the aforementioned methods, Zhao and co-workers utilised Rh(I) as a catalyst to mediate

the Michael addition.[41] The reaction proceeds with catalytic amounts of the hydroxo rhodium complex $[(cod)Rh(OH)]_2$ (1.5 mol %) along with racemic BINAP as ligand (3 mol %) as well as the addition of 1.0 equiv of NaOH (Scheme 39). It is worth mentioning that the selectivities over the Heck product were >99:1.



Scheme 39. Rh-catalysed 1,4-addition of benzoic acids to acryl derivates.

1.5. Conclusions

The last few years have seen the fruitful and fast development of different novel decarboxylative transformations. The use of aromatic carboxylic acids as versatile synthons for the formation of C–C bonds has been successfully demonstrated to be a greener alternative to the traditional cross-coupling reactions. However, to completely compete with the current methodologies, several challenges must be addressed:

- The great majority of decarboxylative cross-couplings reported require high reaction temperatures, presenting compatibility problems with sensitive functional groups. Therefore, the development of new methodologies employing milder reaction temperatures is of high priority.
- Catalyst loadings for these transformations must be lowered to be able compete with the extremely low catalyst loadings currently employed in the cross-coupling field.

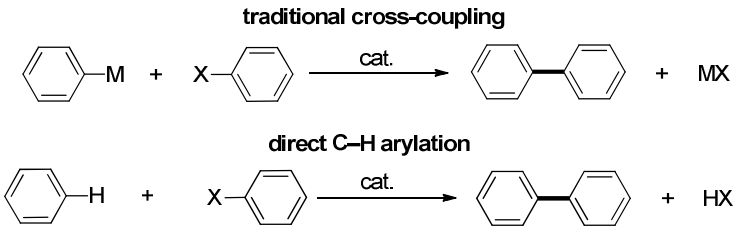
- Also, a complete understanding of the decarboxylation mechanism is of high importance, which would provide insight for more efficient methodologies employing new catalyst systems.
- In the cases where decarboxylative methods are combined with C−H activation based methodologies, the use of only O_2 to reoxidise the catalyst would be extremely beneficial. The generation of CO_2 and H_2O as the only byproduct would imply a tremendous step forward in the field of cross-couplings placing them amongst the greenest reactions in organic chemistry.

Chapter 2. Intermolecular decarboxylative direct C3 arylation of indoles with benzoic acids[i]

2.1. Introduction

2.1.1. C−H arylation

As discussed in chapter 1, C−H activation based methodologies have emerged in the last decades as an alternative to traditional cross-couplings (Scheme 40).[42]

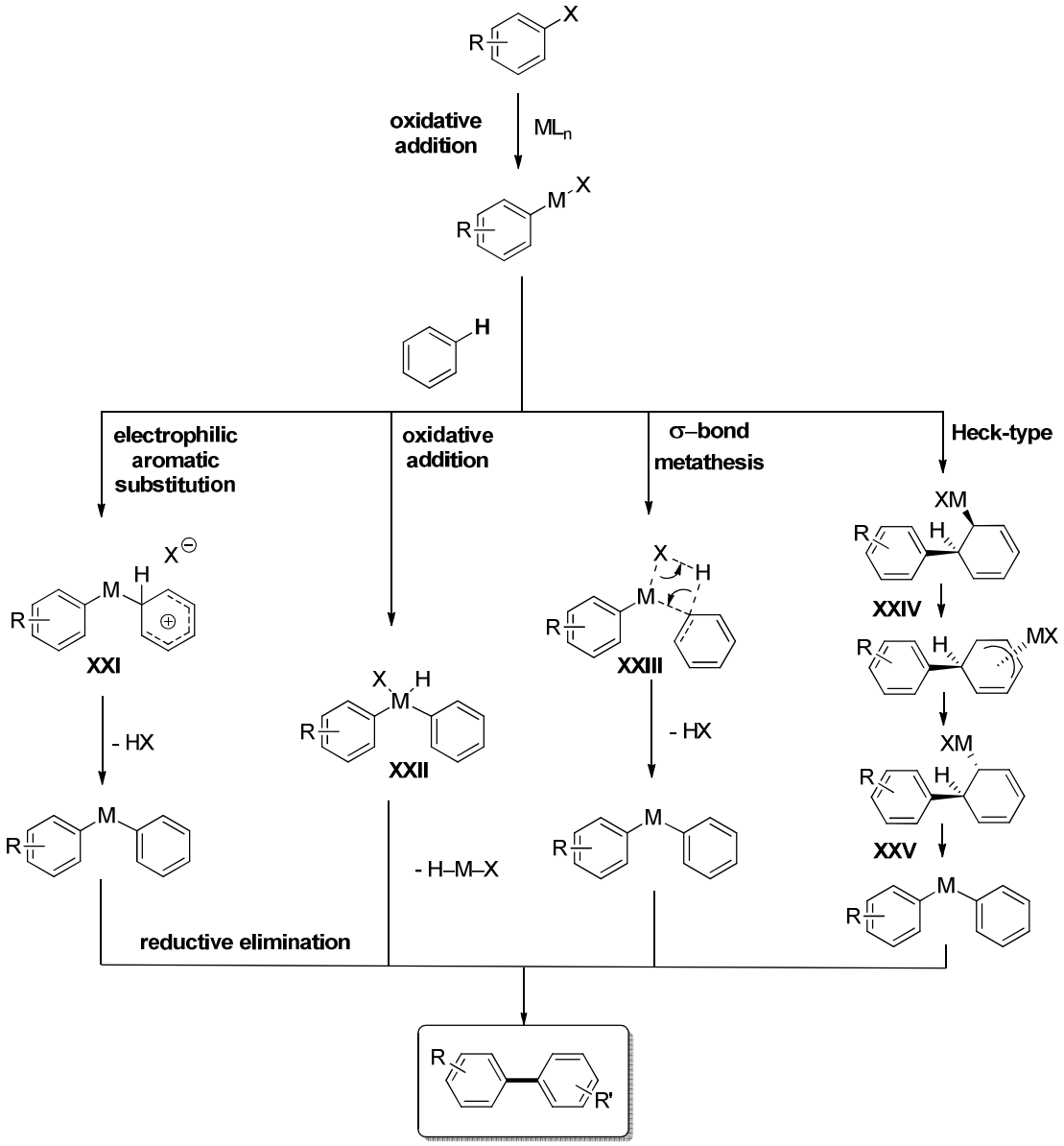


Scheme 40. Traditional cross-coupling versus direct C−H arylation.

This group of methodologies are generally referred as C−H arylation methodologies, whereas the term "C−H activation" is usually referred to the step in which an 'inert' C−H bond is 'activated' by transforming it into a reactive C−M bond (Carbon−Metal bond).

Mechanistically, it is believed that the direct arylation of arenes occurs via oxidative addition of the transition metal into the aryl halide, followed by one of a number of possible key pathways for the C−H activation step (Scheme 41).

[i] Part of this work was developed in collaboration with Dr Pengfei Lu (PDRA, Queen Mary University of London). Dr Lu's contribution will be made explicit where relevant.



Scheme 41. Different mechanisms for the metal-catalysed direct arylation of arenes. Ligands on the metal were omitted for clarity.

The aryl-metal species formed after the oxidative addition can undergo C−H activation through four different pathways:

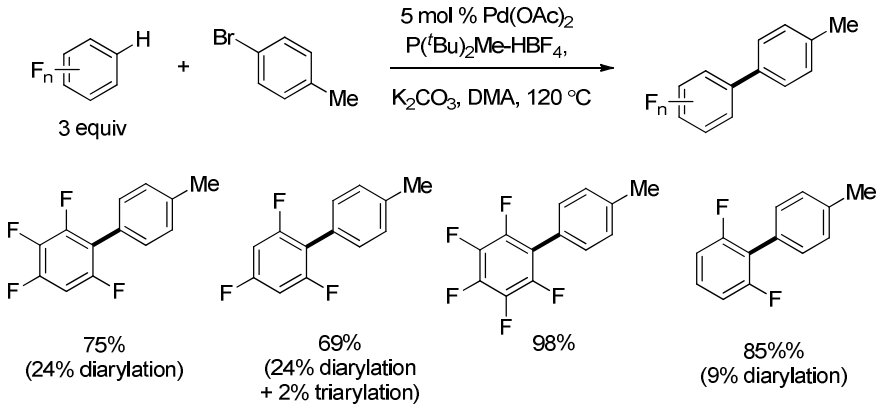
- Electrophilic aromatic substitution; the arene attacks the metal center displacing an anionic ligand to form the Wheland intermediate **XXI**. Subsequent rearomatisation forms the C−M bond.
- Oxidative addition; the metal undergoes oxidative addition into the C−H bond to form metal hydride species **XXII**.

- σ−bond metathesis or concerted-metalation-deprotonation (CMD); The C−M bond is formed through the transition state **XXIII**.
- Heck-type mechanism; in this case, the aryl-metal species undergo carbometalation into one of the double bonds of the arene to form intermediate **XXIV**. At this stage, an anti β-hydride elimination could take place to form the C−M bond. On the other hand, **XXIV** could isomerise affording **XXV**, and undergo a simple β-hydride elimination.

It is noteworthy that differences on the substrate, transition metal, solvent, base or ligands for a given transformation, may lead to different C−H activation mechanisms.[42]

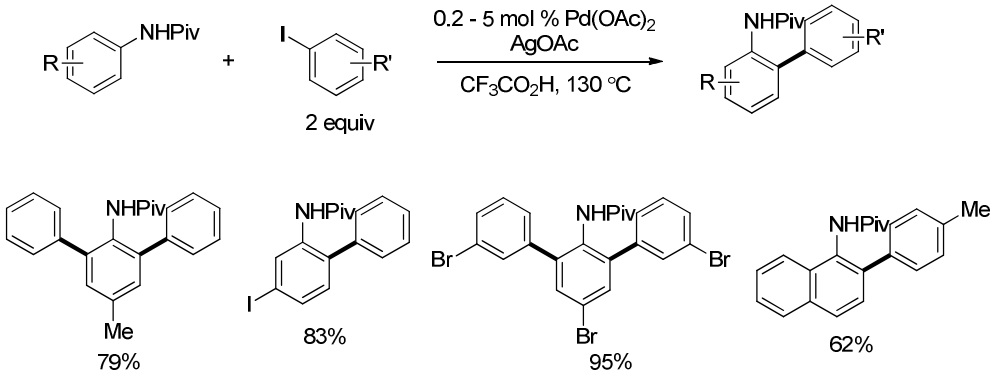
In C−H arylation methodologies with haloarenes, the formation of an organometallic reagent is avoided, thereby reducing synthetic steps in the process. Since no organometallic partner is needed, the overall waste of the process is also minimised.

To illustrate the application of such methodologies, two examples are shown in Scheme 42 and 43. For example, the direct arylation of fluorinated arenes was achieved by Fagnou and co-workers allowing excellent yields of the desired biaryl compounds.[43]



Scheme 42. Pd-catalysed direct arylation of fluorinated arenes.

Another example is Daugulis' protocol for the direct arylation of phenylpivalamides with aryl iodides (Scheme 43).[44]

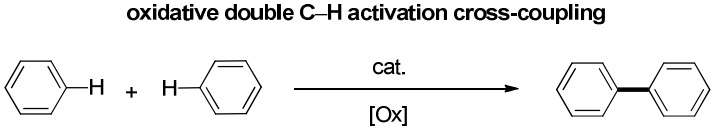


Scheme 43. Pd-catalysed direct arylation of phenylpivalamides.

Although C–H arylation methodologies address the main issues regarding the traditional cross-coupling, they still present the challenge of controlling the regioselectivity. Hence, when more than one C–H bond is present in the starting material, several regioisomers might be obtained as the final product (Scheme 42 and 43). Another implicit drawback of C–H arylation is the harsh conditions required for the C–H activation step often leading to high reaction temperatures.

2.1.2. Oxidative double C−H activation cross-couplings

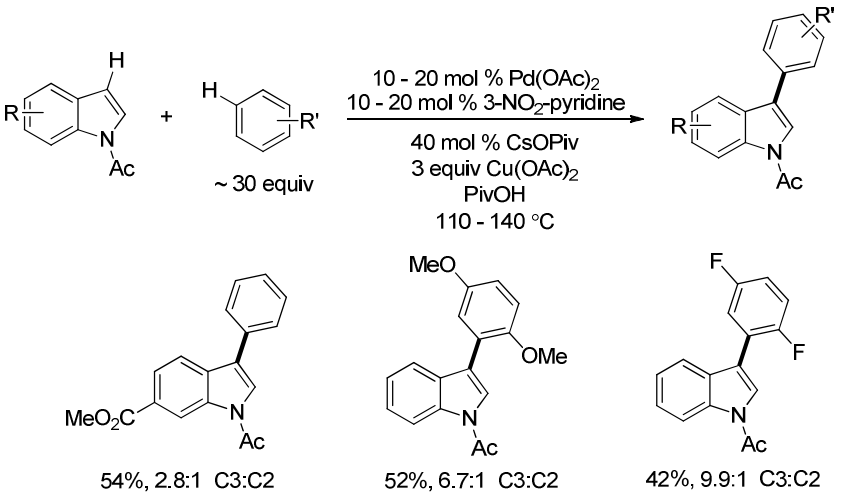
Building upon C−H arylation methodologies, oxidative double C−H arylation cross-couplings have recently emerged for the formation of $C(sp^2)$−$C(sp^2)$ bonds. This approach provides biaryl structures without the use of aryl halides or organometallic reagents (Scheme 44).



Scheme 44. Oxidative double C−H activation cross-coupling or dehydrogenative cross-coupling.

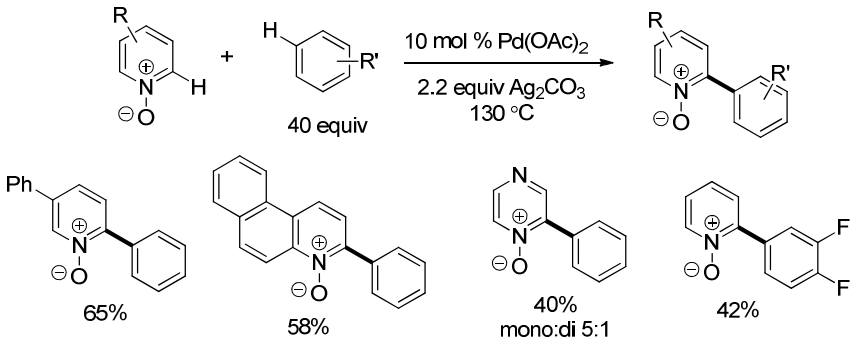
Oxidative double C−H activation cross-couplings benefit from lower cost and waste when compared to traditional cross-coupling or C−H arylation methodologies. Therefore, this strategy has captivated chemists' interest, as evidenced by the many advances in this particular area in recent years.[45] A selection of the most notable advances is exemplified in Schemes 45 and 46.

The first oxidative double C−H cross-coupling was reported by Fagnou and coworkers, showing the possibility of arylating indoles with simple arenes via a tandem C−H activation process (Scheme 45).[46]



Scheme 45. Pd-catalysed oxidative arylation of indoles.

In another account, Chang and co-workers developed conditions for the oxidative cross-coupling of azine *N*-oxides with arenes (Scheme 46).[47]



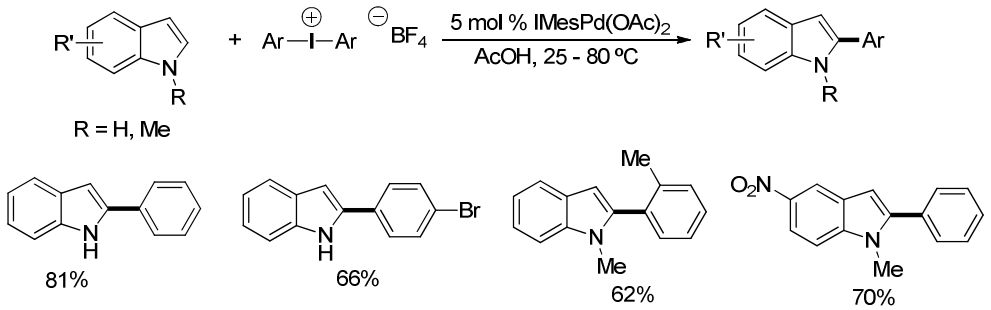
Scheme 46. Pd-catalysed oxidative arylation of azine *N*-oxides.

However, despite the atom- and step-economy of these methodologies, several challenges still need to be addressed. In addition to the aforementioned problems for C−H activation based methodologies, double oxidative transformations usually require a large excess of one of the coupling partners (20 – 50 equiv) to avoid the formation of homocoupling byproducts. Moreover, the control of the regioselectivity in this strategy is exacerbated because of the larger number of potential C−H bonds that could be activated.

2.1.3. Direct arylation of indoles

Indoles are arguably the most abundant heteroarene structure in natural products and other biologically active compounds.[48] Therefore, significant effort has been focused towards the direct arylation of this heterocycle.

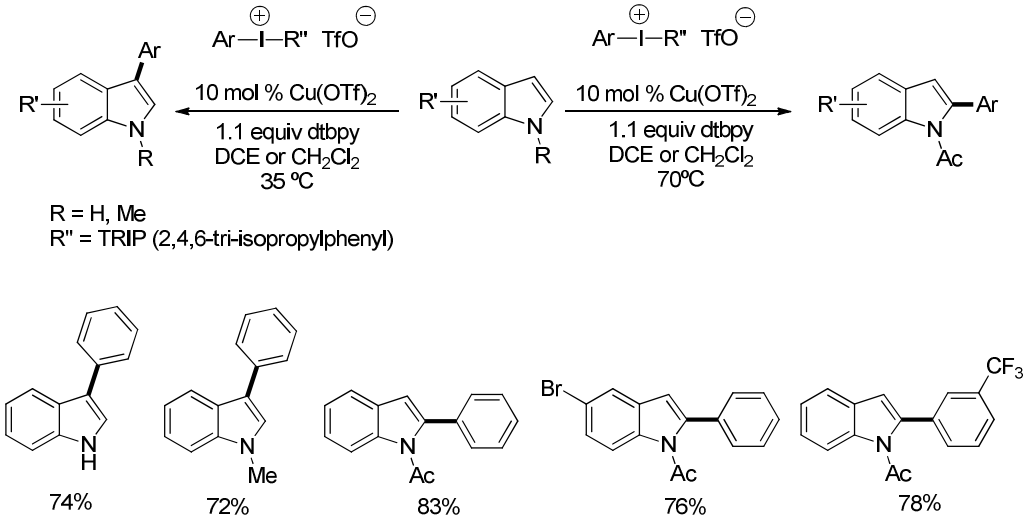
Indeed, several C−H activation based methodologies have been reported;[49] however, the greater majority still suffer from the need for drastic conditions (125 to 150 ºC). Recently, an elegant methodology was reported by Sanford *et al*. which allowed the arylation of indoles at the C2 position, catalysed by Pd, which proceeds at lower temperatures than the previously reported (rt to 80 ºC) (Scheme 47).[49c]



Scheme 47. Pd-catalysed direct C–H arylation of indoles with aryl iodonium(III) species**.**

Subsequently, a Cu-catalysed C−H arylation of indoles was reported by Gaunt *et al*. which proceeds at very mild temperatures (35 to 70 ºC).[50] While Sanford's protocol was limited to C2 arylation of indoles, Gaunt and co-workers successfully achieved a site-selective arylation by tuning the protecting group at nitrogen (Scheme 48).

Therefore, when free-indole or *N*-methylindole are used, exclusive C3 arylation byproducts are obtained. On the other hand, when the nitrogen is protected as an Ac group, the arylation occurs at the C2 position.

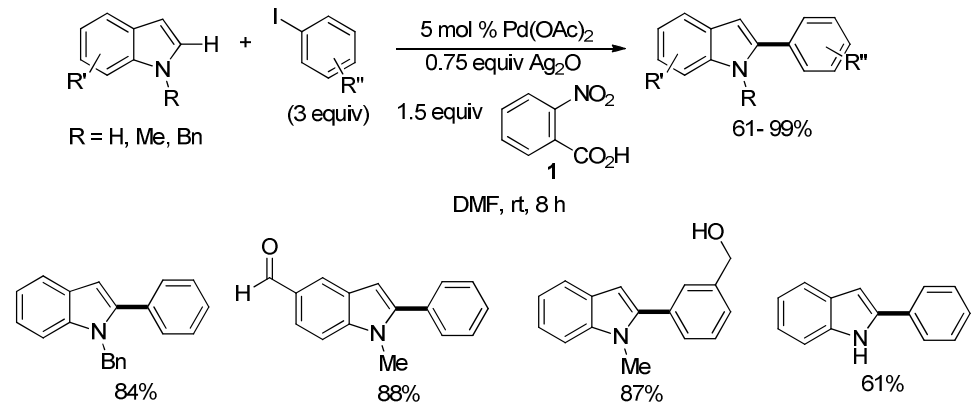


Scheme 48. Cu-catalyzed direct C–H arylation of indoles with bis-aryl iodonium(III) species.

Despite the low temperatures required, both protocols are limited to the use of non-readily accessible iodine(III) arylating agents presenting a synthetic hurdle in the direct C–H arylation of indoles.

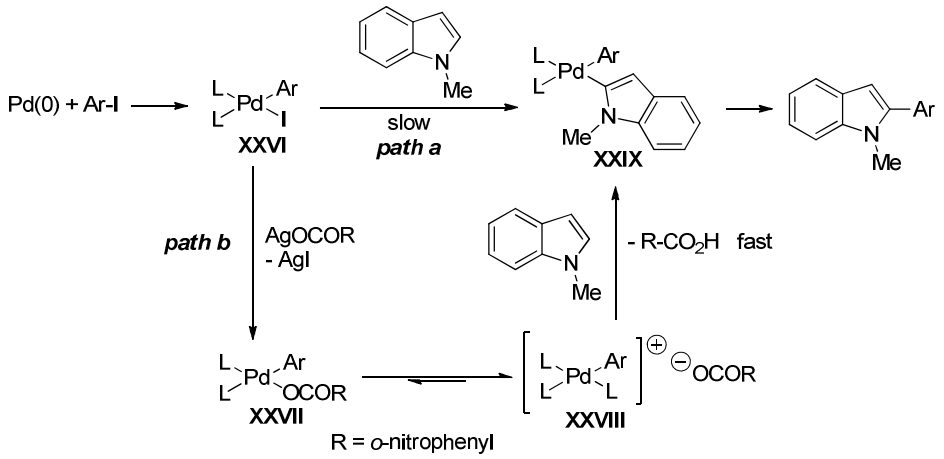
2.2. Previous studies in the group

In the context of C–H activation, our research group has developed a methodology for the direct C–H arylation of indoles using simple aryl iodides (Scheme 49).[51] The reaction proceeds at room temperature, thereby overcoming one of the main drawbacks of C–H arylation. Moreover, the reaction requires only short reaction times (8 h) and it is phosphine-free. Also, the arylation is completely regioselective for the C2 position. These mild conditions allow the use of a wide range of sensitive functional groups such as unprotected phenols and benzylic alcohols, aldehydes, nitriles, etc. The reaction proceeds under Pd catalysis ($Pd(OAc)_2$), with Ag_2O and 2-nitrobenzoic acid as additives.



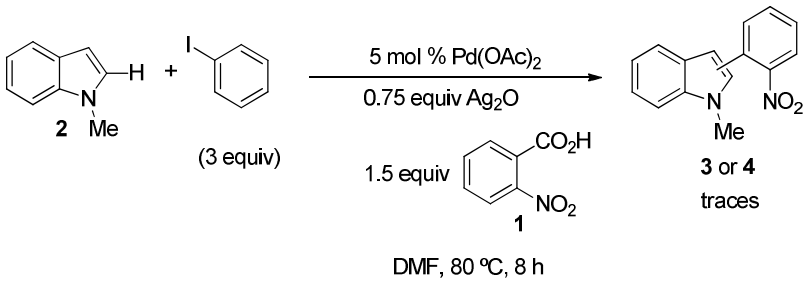
Scheme 49. Pd-catalysed direct C–H arylation of indoles with aryl iodides at room temperature.

The proposed mechanism for the direct C2 arylation of indoles was postulated to proceed via a Pd(0)/Pd(II) catalytic cycle (Scheme 50). Commonly, the limiting step in the arylation of indoles in a Pd(0)/(II) catalytic cycle is believed to be the electrophilic palladation to give the electron-rich Pd(II) species **XXIX** (path a, Scheme 49).[49c] Therefore, since Ag(I) salts are known to abstract halide anions from transition metals, it was reasoned that the use of an appropriate Ag(I) salt to remove iodide from the Pd(II) complex **XXVI**, would generate a cationic Pd species (**XXVIII**), which would be more electrophilic toward the indole unit (Ar′-H) (path b, Scheme 49). Initially, Ag-mediated ligand metathesis of **XXVI** would afford complex **XXVII**. The use of a relatively poorly coordinating carboxylate (2-nitrobenzoate) as the counterion allows the dissociation to the cationic species **XXVIII** in catalytically useful amounts. At the same time, the carboxylate would act as a base in the electrophilic palladation step.



Scheme 50. Proposed mechanism for the Pd-catalysed direct C–H arylation of indoles at room temperature with aryl iodides**.**

During the process of optimisation of the aforementioned protocol, our research group made an interesting observation: when the reaction mixture was heated at temperatures above 80 ºC, the generation of a new byproduct was observed in trace amounts as determined by GCMS (Scheme 51).

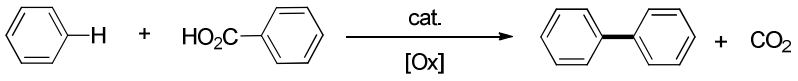


Scheme 51. Preliminary observations.

It was hypothesised that indole derivative (C3 or C2, **3** and **4** respectively) was generated from the coupling of the benzoic acid **1**, presumably via decarboxylation and subsequent coupling to the indole moiety.

2.3. Aims of the project

The observation of traces of the coupling product led us to hypothesise that it should be possible to develop a novel cross-coupling methodology combining both C–H and decarboxylative activations (Scheme 52).

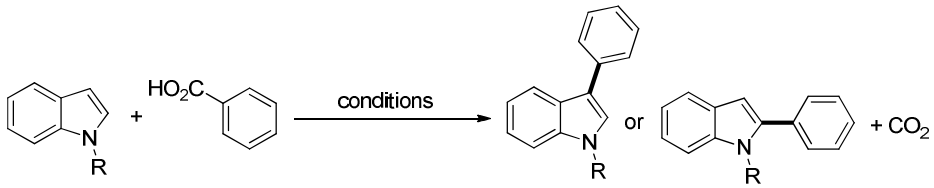


Scheme 52. Decarboxylative C−H arylation.

The combination of such strategies would represent a tremendous step forward in the field since i) there is no need for the prefunctionalisation of any of the coupling partners, ii) benzoic acids are cheap, readily available and stable substrates, and iii) the generation of CO_2 as the main byproduct avoids any halogenated or metal waste.

In contrast to oxidative double C−H activation cross-couplings, decarboxylative direct arylations should allow complete control over the regioselectivity of one of the coupling partners. In addition, since this strategy makes use of two different modes of activation, the formation of homocoupling byproducts should be reduced.

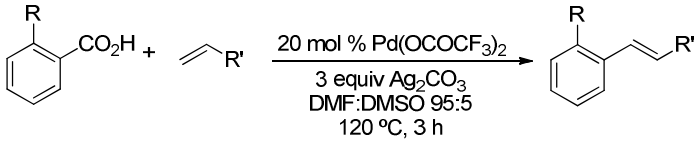
Given the group's previous experience on the C−H arylation of indoles, it was decided to study the system where indoles and benzoic acids are coupled to afford the arylated indole product (Scheme 53). It is worth mentioning that the regioselectivity of this transformation could become an issue to address since two different products (C2 and C3) can be obtained.



Scheme 53. Decarboxylative C−H arylation of indoles.

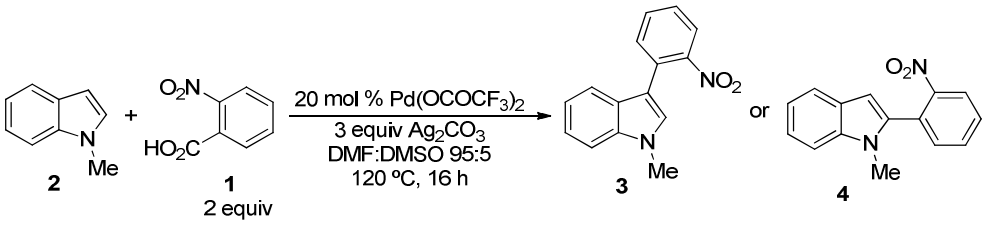
2.4. Optimisation of the decarboxylative direct C–H arylation of indoles

In 2002, Myers *et al*. reported the first decarboxylative Heck-coupling between benzoic acids with styrenes and acrylate derivatives (Scheme 54).[33] The use of substoichiometric amounts of $Pd(TFA)_2$ in combination with Ag_2CO_3 in a mixture of DMF and DMSO (95:5) at 120 ºC afforded the coupling product in very good yields.



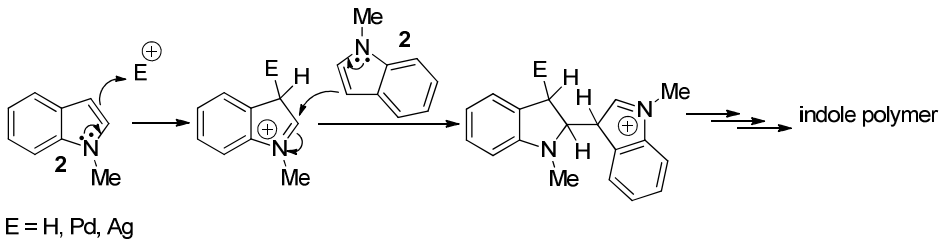
Scheme 54. Myers' decarboxylative olefination.

Due to the similarity with our system, these conditions were chosen as starting point for the optimisation process. Following up the room temperature arylation reported by our research group,[51] *N*-methylindole (**2**) and the 2-nitrobenzoic acid (**1**) were selected as the reagents for the study of the reaction conditions (Scheme 55).



Scheme 55. Decarboxylative direct C–H arylation of indoles with benzoic acids using Myers' protocol.

Unfortunately, when reagents **2** and **1** were subjected to Myers' conditions, no product was observed after 16 h. Moreover, neither indole derivative nor starting material was observed after the reaction. This result led us to hypothesise that the highly reactive *N*-methylindole (**2**) could easily polymerise at high temperatures, leading to consumption of the starting material (Scheme 56).



Scheme 56. Proposed mechanism for the polymerisation of the *N*-methylindole **2**.

In light of this result, we envisaged that by introducing an electron-withdrawing protecting group at the nitrogen of the indole, its nuclophilicity would decrease, thereby reducing the polymerisation side reaction. The results are summarised in Table 1.

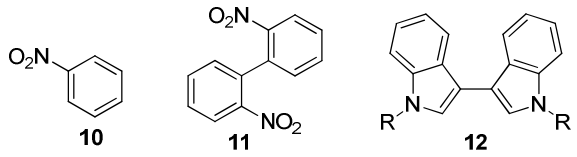
Entry	R	Conversion[b]	Yield of product[a]
1	H, **5**	100%	0%
2	Benzoyl, **6**	59%	0%
3	1-Adamantylcarbonyl, **7**	100%	43%
4	Acetyl, **8**	100%	53%
5	Pivaloyl, **9**	100%	66%

Table 1. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard. [b] Based on recovered starting material.

As depicted in Table 1, unprotected N-H indole **5**, is too reactive under these reaction conditions and failed to give any of the desired coupling product (Table 1, entry 1). Similarl to when *N*-methylindole was used, the non-recovery of the N-H indole substrate or derivatives at the end of the reaction was also attributed to polymerisation

pathways. To our delight, substrates such as **7**, **8** and **9** (Table 1, entries 3, 4 and 5) afforded the coupling product, with the pivaloyl group being the highest yielding. Although *N*-benzoylindole **6** did not afford the desired coupled product, 41% of the starting material was recovered at the end of the reaction.

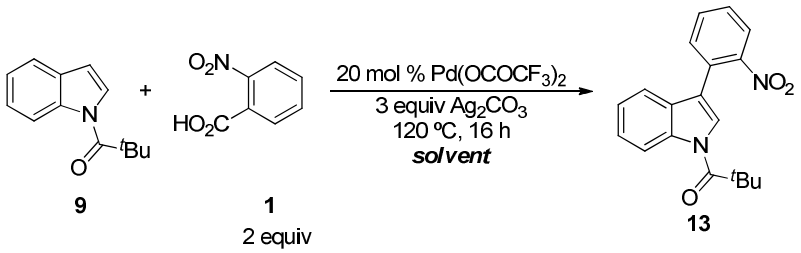
It is worth mentioning at this stage that several byproducts were also detected by GCMS (Scheme 57). The protodecarboxylation of benzoic acid **1** to give **10** is one of the main byproducts in this reaction, as observed by Myers *et al*. in their studies.[33] Also, the formation of homocoupling product from benzoic acid **1** was detected. In addition, small amounts of indole dimerisation product **12** were also detected. The quantification of such byproducts became a major problem due to overlapping of their signals in the ^{1}H NMR spectrum.



Scheme 57. Byproducts observed during the optimisation process.

It is also noteworthy that contrary to the usual C2 regioselectivity observed in most of direct arylation methods,[49] the reaction affords exclusively the C3 arylation product (C2 product is not detected by GCMS or ^{1}H NMR).

We then examined the effect of the solvent in the reaction conditions. Several solvents were tested and a selection of the results is outlined in Table 2.

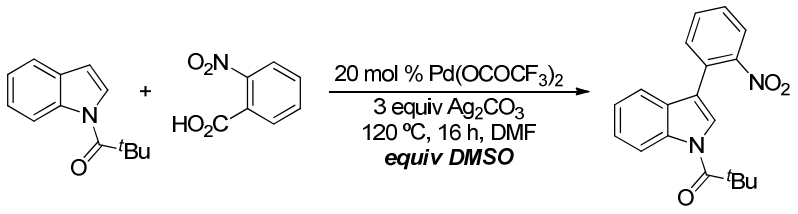


Entry	Solvent	Yield of 13[a]
1	DMF	53%
2	DMF:DMSO 95:5	66%
3	NMP:DMSO 95:5	20%
4	DMA:DMSO 95:5	43%
5	1,4-Dioxane:DMSO 95:5	13%
6	Toluene:DMSO 95:5	-

Table 2. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

It was found that when DMSO is removed from the system, slightly lower yields are obtained (Table 2, entry 1). However, replacing DMF with 1,4-dioxane, NMP or DMA in combination with DMSO, the yields were reduced substantially (entries 3, 4 and 5). Apolar solvents such as toluene failed to give any coupled product **13** (entry 6).

Having settled on DMF:DMSO as the optimum solvent mixture, we then examined the effect of varying the amount of DMSO in the mixture (Table 3). These results suggest that the maximum yield was reached when 2.4 equivalents (per mole of **9**) of DMSO were employed.



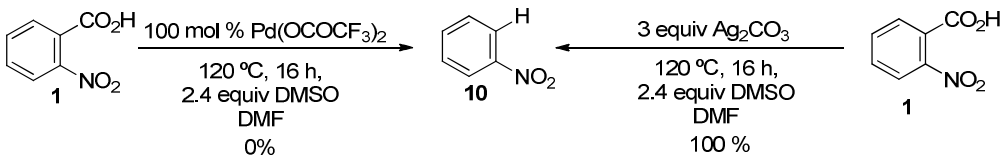
9 **1** 2 equiv **13**

Entry	Equiv DMSO	DMF:DMSO	Yield 13[a]
1	0.8	~99:1	63%
2	1.2	~99:1	66%
3	2.0	98:2	70%
4	2.4	97:3	75%
5	4.0	94:6	63%

Table 3. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

As depicted in Table 3, the amount of DMSO has a remarkable effect on this transformation. Although the role of DMSO in this particular system is still under investigation, it is hypothesised that it could be acting as a ligand for the Ag salt thus affecting the decarboxylation rate of the benzoic acid (*vide infra*).

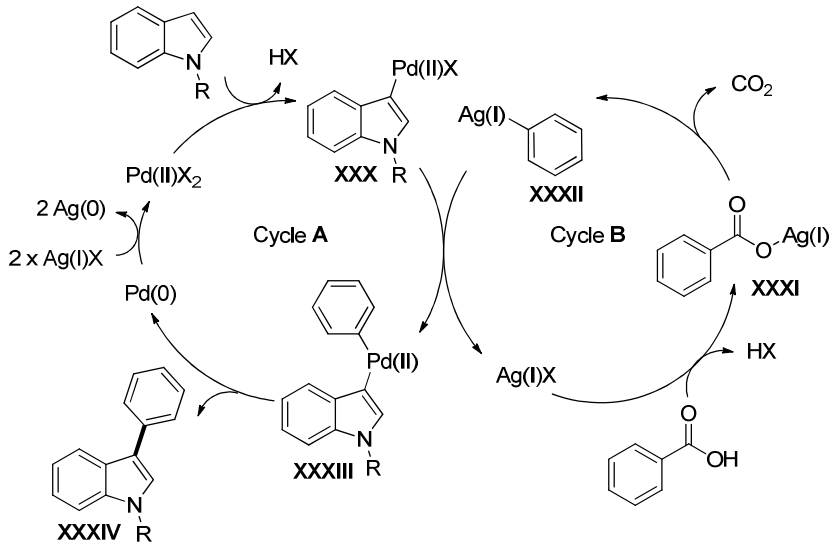
At this stage, and before proceeding further with the optimisation process, attention was focused on the mechanism of the reaction. In 2005, Myers *et al.* published an exhaustive study where it was shown that Pd(II) is responsible for the decarboxylation of the 2,4,5-trimethoxybenzoic acid.[12] The authors also stated that in their methodology Ag_2CO_3 is acting both as the base and the oxidant in their system. However, Ag(I) is a transition metal which could potentially be involved in the decarboxylation process. Therefore, experiments into the decarboxylation step were performed. 2-Nitrobenzoic acid (**1**) was then subjected to a variety of decarboxylation reaction tests with the aim of elucidating the role of each metal. The results of the experiments are outlined in Scheme 58.



Scheme 58. Protodecarboxylation of **1** under in the presence of Pd or Ag salts.

When Ag_2CO_3 was absent in the system, and 100 mol % of $Pd(TFA)_2$ was used, no decarboxylated product was observed and starting material was recovered (Scheme 58). However, when 3 equivalents of Ag_2CO_3 were used instead, in the absence of any Pd(II) source, surprisingly, a quantitative yield of 2-nitrobenzene **10** was obtained. This unexpected result suggests that, in our decarboxylative direct C–H arylation, Ag(I) is responsible not only for the oxidation of the Pd(0) to Pd(II) but also for the decarboxylation of the 2-nitrobenzoic acid **1**. In light of these observations, a plausible mechanism for the C–H arylation of indoles was postulated (Scheme 59).[ii] A dual catalytic cycle is suspected to operate in this transformation. Catalytic cycle A is driven by the Pd catalyst. Ag(I), on the other hand, is operating the other catalytic cycle, which is responsible for the decarboxylation of the benzoic acid. Initially, Pd(II) undergoes electrophilic aromatic palladation to form the indolyl-Pd(II) species **XXX**. Conversely, Ag(I) carboxylate **XXXI** generates the aryl-Ag(I) intermediate **XXXII** with the release of a molecule of CO_2. Transmetalation of **XXXII** with **XXX** forms the bis-aryl-Pd(II) species **XXXIII**, which after reductive elimination affords the desired product **XXXIV** with concomitant formation of Pd(0). To close cycle A, Ag(I) salts reoxidise Pd(0) to Pd(II).

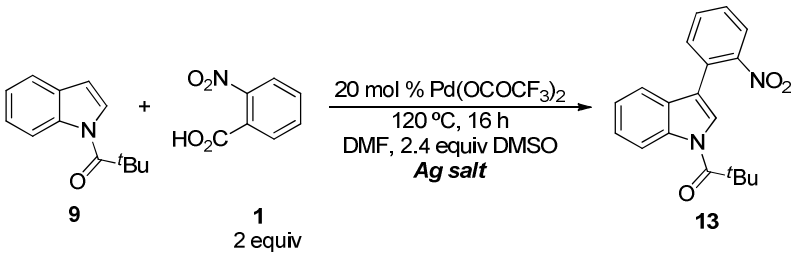
[ii] The regioselectivity of the reaction will be discussed in Section 2.8.



Scheme 59. Proposed mechanism for the decarboxylative C–H arylation of indoles with benzoic acids.

It is worth mentioning that experimental evidence for the formation of the aryl-Ag(I) intermediate was unobtainable. This difficulty has been corroborated by several reports, which show the extreme sensitivity of these compounds even at room temperature and the difficulty of their characterisation.[52]

Having demonstrated that Ag(I) was necessary for the decarboxylation (Scheme 56), several Ag(I) salts, in place of Ag_2CO_3, were tested. Since 3 equiv of Ag_2CO_3 (6 equiv of Ag(I)) were used during the optimisation process, the same amounts of Ag(I) ions were used. Table 4 is a brief summary of the Ag(I) salt screen.

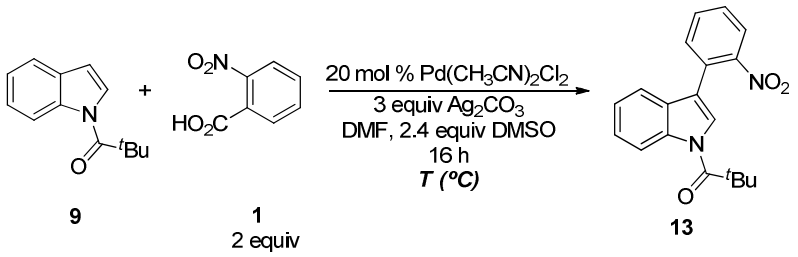


Entry	Equiv Ag salt	Yield 13[a]
1	Ag_3PO_4 (2 equiv)	-
2	Ag_2O (3 equiv)	-
3	AgTFA (6 equiv)	37%
4	AgOAc (6 equiv)	46%
5	Ag_2CO_3 (3 equiv)	75%

Table 4. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

Ag_2O and Ag_3PO_4 failed to give any product, giving instead large amounts of protodecarboxylation (Table 4, entries 1 and 2). However, AgTFA and AgOAc satisfactorily produced reasonable amounts of the desired coupling product (Table 4, entries 3 and 4), although Ag_2CO_3 was still yielding the best results under these particular conditions (Table 4, entry 5).

In a parallel study conducted by another member of the research group,[i] different Pd catalysts were tested in the decarboxylative C–H arylation of indoles. It was found that $Pd(CH_3CN)_2Cl_2$ led to better yields compared with $Pd(TFA)_2$ when applied to 2-chloro-5-nitrobenzoic acid **20** (see Table 9). Therefore, this catalyst was tested in our system although only 56% of the coupled product **13** was obtained. However, in spite of the lower yields, the optimisation of the temperature and the concentration were carried out with the aforementioned catalyst ($Pd(CH_3CN)_2Cl_2$). Hence, different temperatures were tested for the reaction and results are summarised in Table 5.

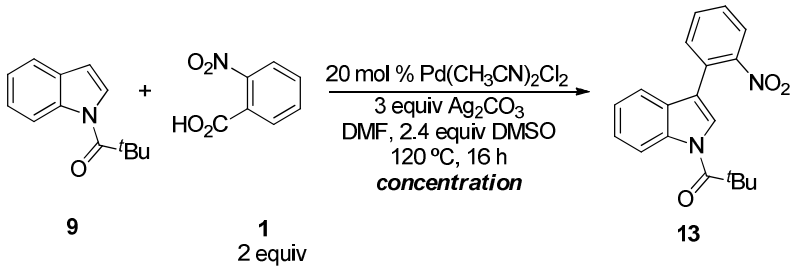


Entry	T (ºC)	Yield 13[a]
1	110	42%
2	120	56%
3	130	30%

Table 5. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

It is important to mention that the temperature is a key parameter in this transformation. Small differences in temperature will lead to variations on the rate of decarboxylation of the Ag(I) carboxylate **XXXI** as well as transmetalation/decomposition of intermediate **XXXII** (Scheme 59). Indeed, as shown in Table 5, a simple variation of 10 ºC dramatically reduced the yield of **13**.

The concentration of the reaction was also optimized, highlighting 0.2 M as the optimum (Table 6).



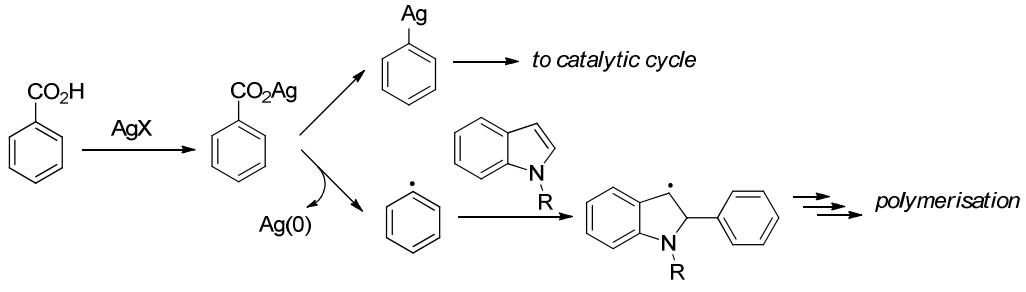
Entry	Concentration of DMF	Yield 13[a]
1	0.4 M	43%
2	0.2 M	52%
3	0.1 M	35%

Table 6. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

At this stage, the catalyst was switched back to $Pd(TFA)_2$ and the amount of catalyst was optimised. Lower amounts of Pd catalyst were tested but the overall yield was substantially lower. Since higher amounts of catalyst are not ideal, 20 mol % of $Pd(TFA)_2$ was deemed to be a reasonable amount of catalyst for further studies.

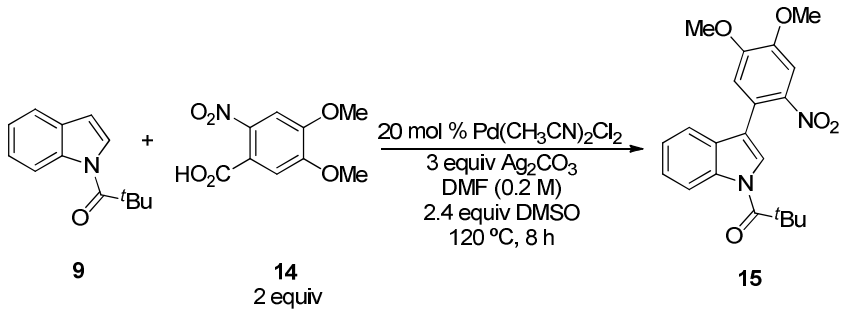
2.5. Studies on the decomposition of the starting material

During the process of optimisation it was found that around 30-35% of the indolic starting material was transformed to an unknown and unobserved compound. As mentioned before, this was attributed to polymerisation products when *N*-methylindole (**2**) was used instead. However, it was hypothesised that the *N*-pivaloylindole (**9**) should be far less reactive than *N*-alkylindoles and therefore, its polymerisation should be reduced, if not avoided. Hence, when *N*-pivaloylindole (**9**) was stirred at 120 ºC for 16 h in the presence of 20 mol % $Pd(TFA)_2$, 90% of the starting material was recovered. Approximately 5% dimerisation of the indole to **12** was also observed. This experiment led us to discard the idea of starting material polymerisation. However, the in situ deprotection of the pivaloyl group in a basic medium at high temperatures followed by polymerisation could not be ruled out. Since Ag(I) ions are sensitive to sunlight, decomposition by a radical process to give Ag(0) was also suspected.[53] Therefore, it was hypothesised that the presence of this metal in the system might lead to the formation of radical species, which can trigger a chain reaction such as the one depicted in Scheme 60.



Scheme 60. Proposed radical mechanism for the polymerisation of the indole material.

To test the hypothesis of radical formation, two different radical scavengers were added into the reaction of the *N*-pivaloylindole **9** and the 4,5-dimethoxy-2-nitrobenzoic acid (**14**), using $Pd(CH_3CN)_2Cl_2$ as the catalyst. The results are summarised in Table 7.



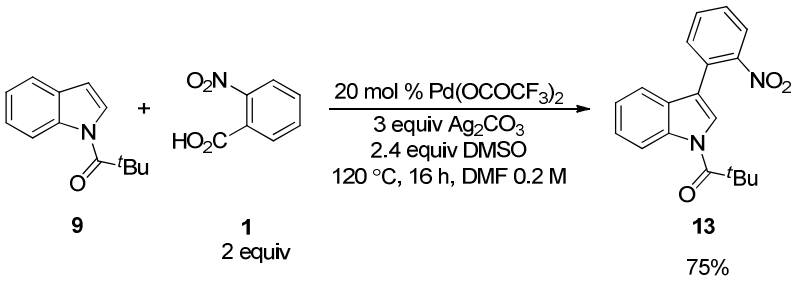
Entry	Radical scavenger	Yield 15[a]	Indole dimer[a]	9 (recovered)[a]
1	-	40%	10%	-
2	TEMPO (1 equiv)	40%	9%	51%
3	Ascorbic acid (1 equiv)	0	0	100%

Table 7. [a] Yields determined by ^{1}H NMR using mesitylene as internal standard.

After 8 hours of reaction, all the indolic material was recovered when TEMPO or ascorbic acid were added (Table 7, entries 2 and 3). However, in the control experiment, no remaining starting material was observed (Table 7, entry 1). Unfortunately, the addition of TEMPO did not increase the yield of product **15** when compared with the control experiment. On the other hand, when ascorbic acid is added, 100% of the starting material **9** was recovered. These results led us to hypothesise that the formation of radicals is indeed occurring in a parallel detrimental pathway.

Variation of the stoichiometry of TEMPO at different reaction times did not lead to any increase in the yield of coupling product **13**.

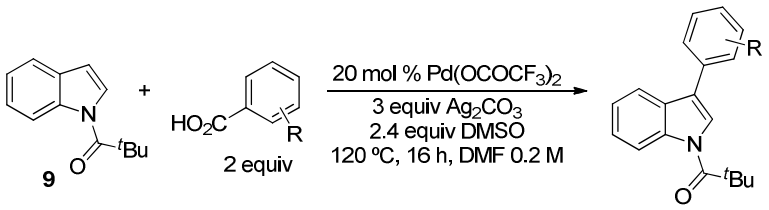
In conclusion, the best conditions found for the coupling of *N*-pivaloylindole (**9**) and 2-nitrobenzoic acid (**1**) are outlined in Scheme 61.



Scheme 61. Optimised conditions for the direct arylation of **9** with **1**.

2.6. Scope of the decarboxylative direct C–H arylation of indoles

Initially, we tested the effect of changing the NO_2 substituent to the *meta* and *para* positions (Table 8, entry 1 and 2). Disappointingly, no reaction was observed in these cases, nor in the absence of the NO_2 group (Table 8 entry 3). On the other hand, replacing the electron-withdrawing nitro group with the electron-donating MeO group resulted in a very low yield of the aryl indole product.



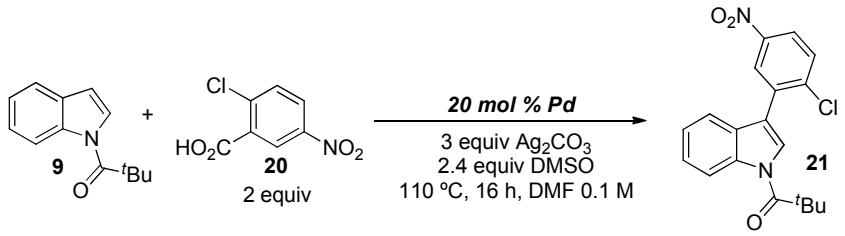
Entry	Benzoic acid	Yield of product[a]	9 recovered[a]
1	3-Nitrobenzoic acid (**16**)	-	90%
2	4-Nitrobenzoic acid (**17**)	-	96%
3	Benzoic acid (**18**)	-	99%
4	2,4-Dimethoxybenzoic acid (**19**)	9%	75%

Table 8. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

It is noteworthy that in all cases starting material **9** was recovered almost completely. The fact that no decomposition of the starting material was observed in these cases, suggests that no deprotection of the pivaloyl group of **9** occurs in the reaction conditions.

It was then hypothesised that an electron-withdrawing group in the *ortho*-position was necessary in this particular system for a successful coupling with the *N*-pivaloylindole (**9**).

As mentioned before, Dr Lu optimised the conditions for the coupling with 2-chloro-5-nitrobenzoic acid (**20**) resulting in the use of $Pd(CH_3CN)_2Cl_2$ at 110 ºC in DMF 0.1 M as the optimum conditions for this transformation (Table 9).

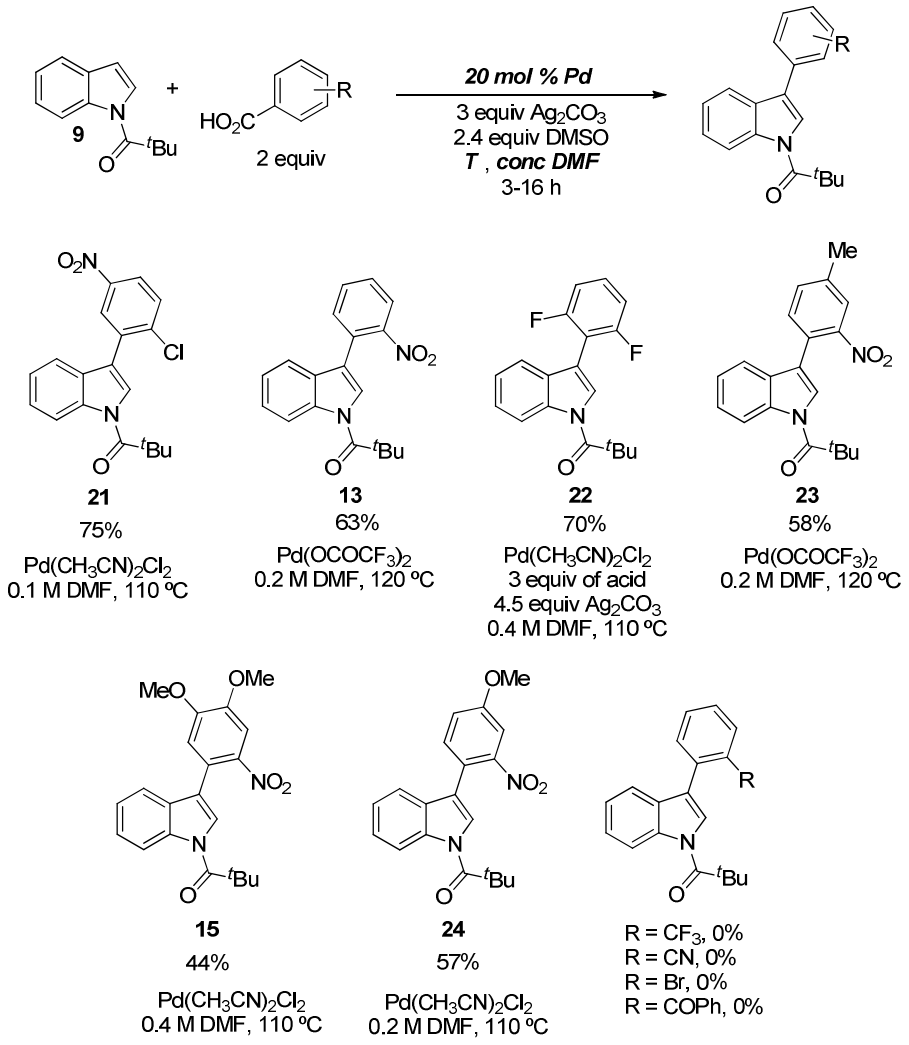


Entry	Pd catalyst	Yield 21[a]
1	$Pd(OCOCF_3)_2$	72%
2	$Pd(dppf)Cl_2$	25%
3	Pd-PEPPSI-IPr	62%
4	$Pd(CH_3CN)_2Cl_2$	77%

Table 9. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

The requirement for slightly modifying concentration, temperature and catalyst to obtain high yields with the 2-chloro-5-nitrobenzoic acid (**20**), reflects a general trend when the protocol was applied to different benzoic acids. Therefore, for each benzoic acid tested, a small adjustment of these three parameters was necessary to find the optimum conditions.

A summary of the different *ortho* substituted benzoic acids with electron-withdrawing groups tested in the decarboxylative C–H arylation of *N*-pivaloylindole (**9**) is shown in Scheme 62.



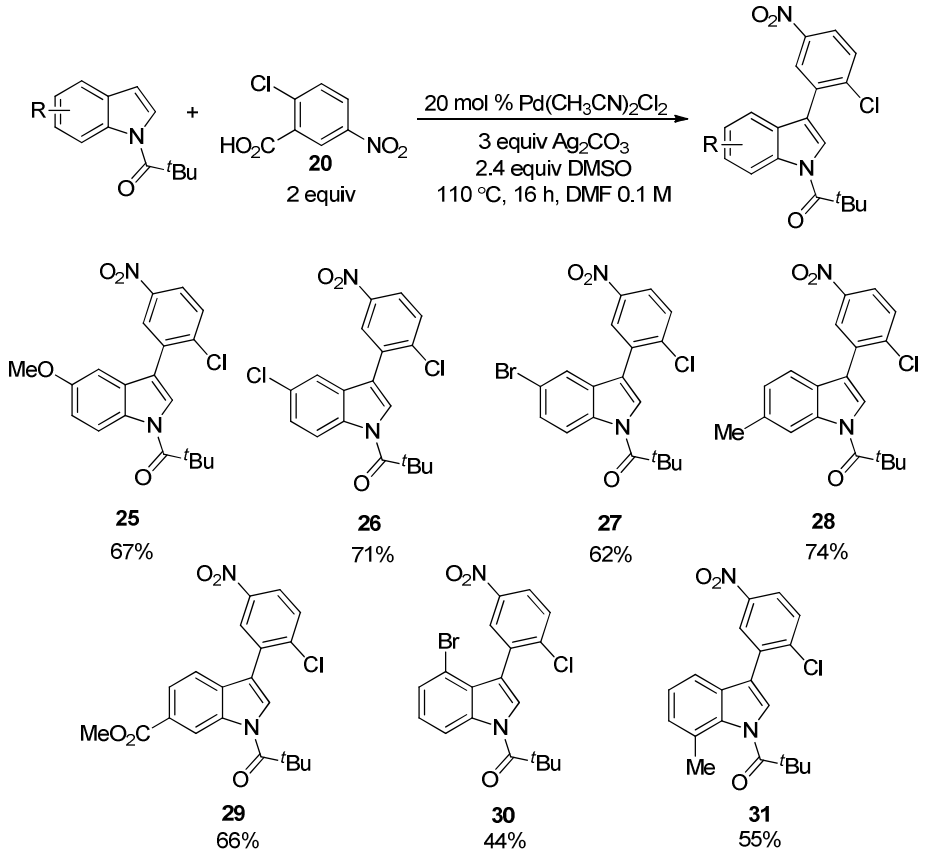
Scheme 62. Scope of the decarboxylative direct C–H arylation of indoles. Yields of isolated pure material.

Unfortunately, only benzoic acids with very electron-withdrawing *ortho* substituents such as NO_2, Cl, or F, led to coupling products in moderate to excellent yields under the reaction conditions. It is noteworthy that the protocol allowed the presence of electron-donating groups at other positions in the benzene ring. However, other acids tested bearing CF_3, CN, Br or COPh at the *ortho* position failed to react.

It is worth mentioning that when these reactions were scaled-up to 1 mmol scale, lower yields were obtained in some cases (e.g. 2-nitrobenzoic acid (**1**) and 4,5-dimethoxy-2-nitrobenzoic acid (**14**) afforded 75% and 52% yield of coupled product, respectively, at 0.125 mmol scale). This could be due to an increase of the moisture

on the reaction conditions leading to a fast protodecarboxylation of the benzoic acids, different stirring rates, etc. Therefore, further optimisation may be required in order to scale-up this methodology.

Once the benzoic acid scope was screened, focus was turned to the effect of the substitution on the indole moiety. The results are outlined in Scheme 63.



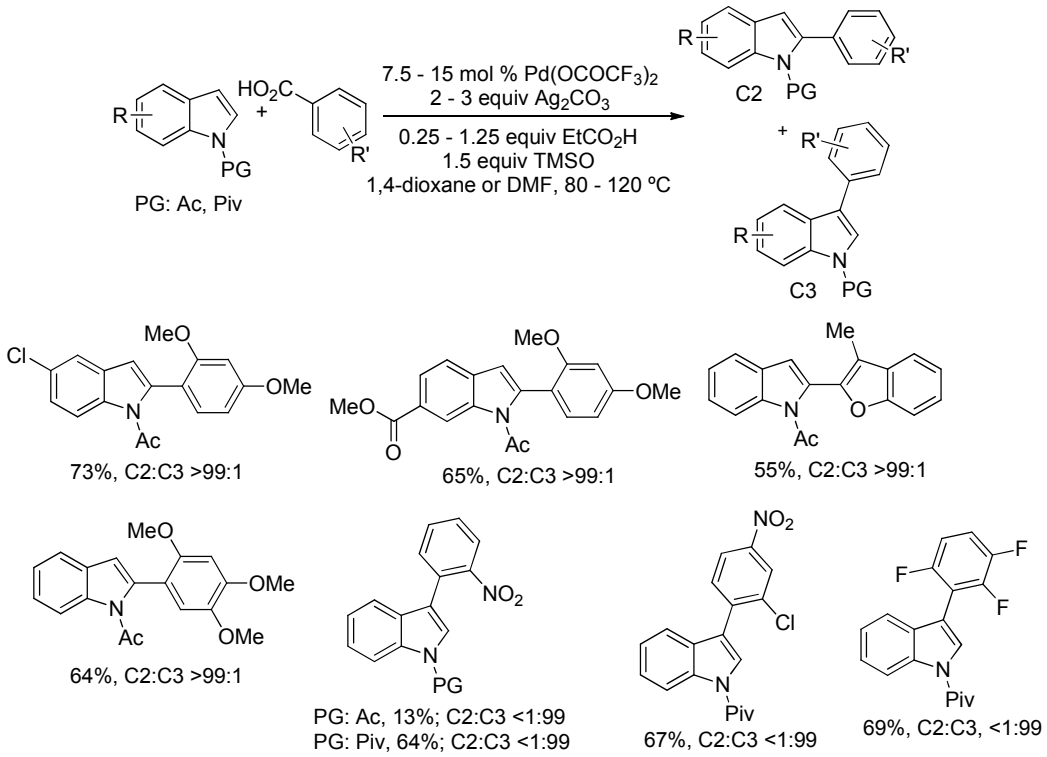
Scheme 63. Scope of the decarboxylative direct C–H arylation of indoles. Yields of isolated pure material.

Gratifyingly, several indoles were successfully coupled, with no need for modification of the standard reaction conditions. Indoles bearing MeO, Br, Cl, Me or CO_2Me groups at the C5 and C6 positions, were tolerated under the reaction conditions giving excellent yields of the coupling products (**25** to **29**). It is noteworthy that even highly hindered indoles substituted in C4 and C7 afforded moderate to good yields of the coupling adducts without further optimisation of the reaction conditions (**30** and **31**). It is also worth mentioning that no changes in the regioselectivity were

observed in any case and all adducts were arylated at the C3 position, even for the more hindered substrate **30**.

2.7. Recent examples of decarboxylative C−H arylation protocols

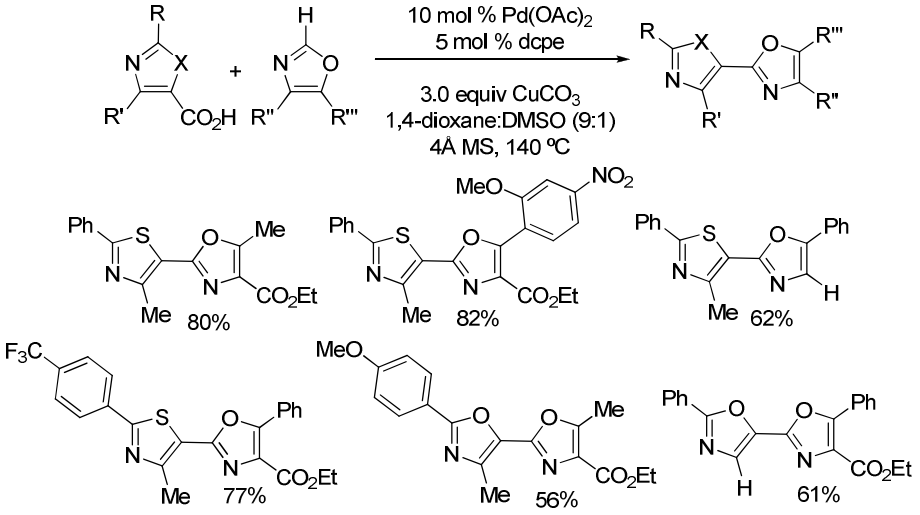
Building upon the work described in this chapter, several other research groups have reported a wide range of different decarboxylative C−H arylation methodologies. For example, an extensive study on the decarboxylative C–H arylation of indoles was reported by Su *et al*.[54] Therein, the authors present a methodology for the arylation of indoles at the C2 or C3 position in a regioselective fashion (Scheme 64). The authors state that the addition of propionic acid and TMSO (tetramethylenesulfoxide) is crucial to obtain good yields of the desired product.



Scheme 64. Selective C2 and C3 decarboxylative direct C–H arylation of indoles.

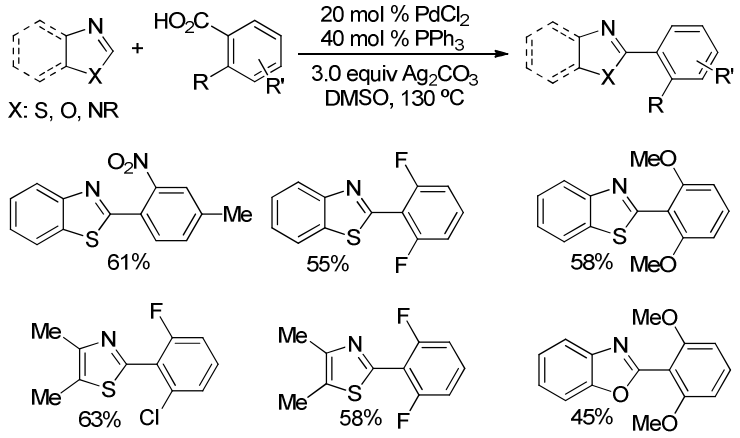
Subsequently, Greaney and co-workers extended the decarboxylative C–H arylation concept to heteroaromatic carboxylic acids.[55] The work reported the direct arylation

of azoles and thiazoles using azole- and thiazole-carboxylic acids as coupling partners. $Pd(OAc)_2$ (10 mol %) and the bidentate phosphine dcpe (5 mol %), together with stoichiometric $CuCO_3$ permits a successful coupling of a wide variety of azoles and thiazoles (Scheme 65).



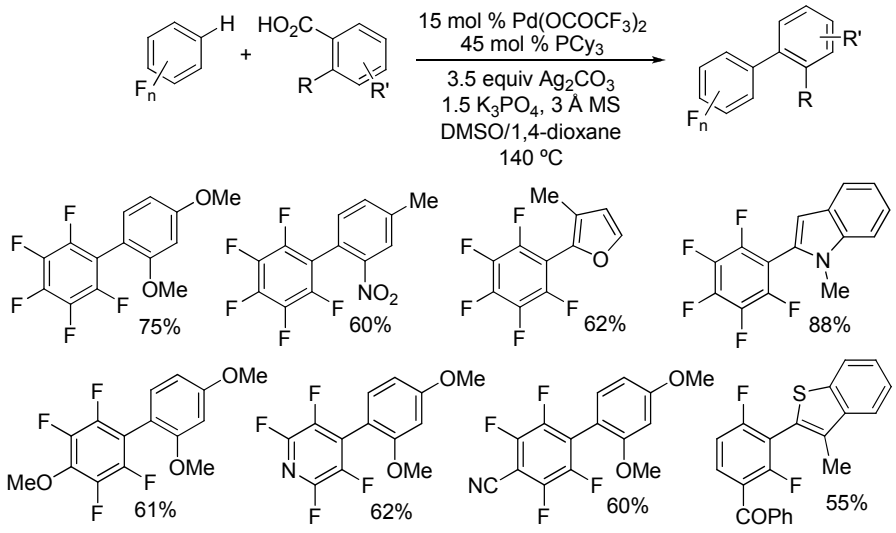
Scheme 65. Decarboxylative C–H arylation of azoles and heteroaromatic carboxylic acids.

The arylation of heteroaromatic compounds has also been studied by Tan *et al.* As a result, the arylation of benzoxazoles, thiazoles or benzothiazoles was reported. [56] Such heteroarenes were successfully arylated with benzoic acids bearing an *ortho* electron-withdrawing or -donating group using $PdCl_2$, PPh_3 and Ag_2CO_3 (Scheme 66).



Scheme 66. Decarboxylative C−H arylation of heteroarenes.

Tan *et al.* also reported a few examples of the arylation of polyfluorinated arenes with benzoic acids in this same report.[56] However, such arylations were exhaustively studied by Su *et al.*[57] Su and co-workers reported a catalytic system based on Pd(II)/PCy_3 with the use of Ag_2CO_3 and K_3PO_4 allowing the coupling of a wide range of polyfluoroarenes with a great variety of electron-withdrawing and -donating benzoic acids (Scheme 67).



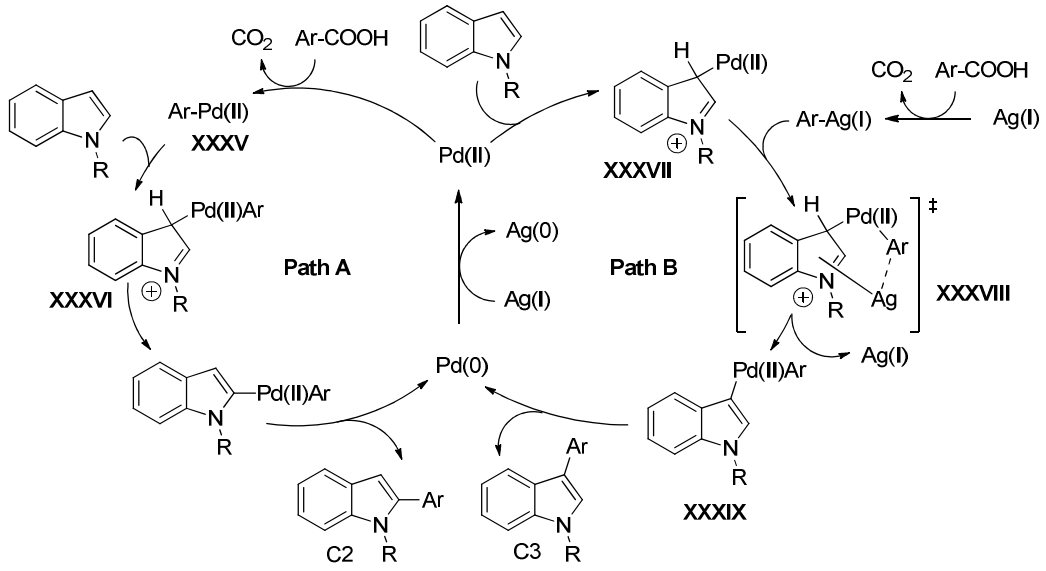
Scheme 67. Decarboxylative C−H arylation of polyfluorinated arenes.

2.8. Discussion on the regioselectivity of the C–H arylation of *N*-pivaloylindoles

The mechanistic pathway of Pd-catalysed decarboxylative methodologies which leads to regioselective arylations at either C2 or C3 positions on the *N*-pivaloylindole has not been fully elucidated yet. However, in this section different hypotheses and plausible mechanisms for this regioselectivty are discussed.

As mentioned previously, Su *et al.* developed a related protocol for a selective direct C–H arylation of indoles with benzoic acids (Scheme 64).[54] In their work, exclusive selectivity was observed either at C2 or C3 when *N*-pivalyolindole was utilised. The authors stated that this selectivity depends only on the nature of the benzoic acid employed as coupling partner. When electron-rich benzoic acids were used, complete C2 arylation was observed. However, when electron-deficient benzoic acids were employed, C3 selectivity was achieved (consistent with our protocol). In light of these

observations, the authors postulated the mechanism depicted in Scheme 68.



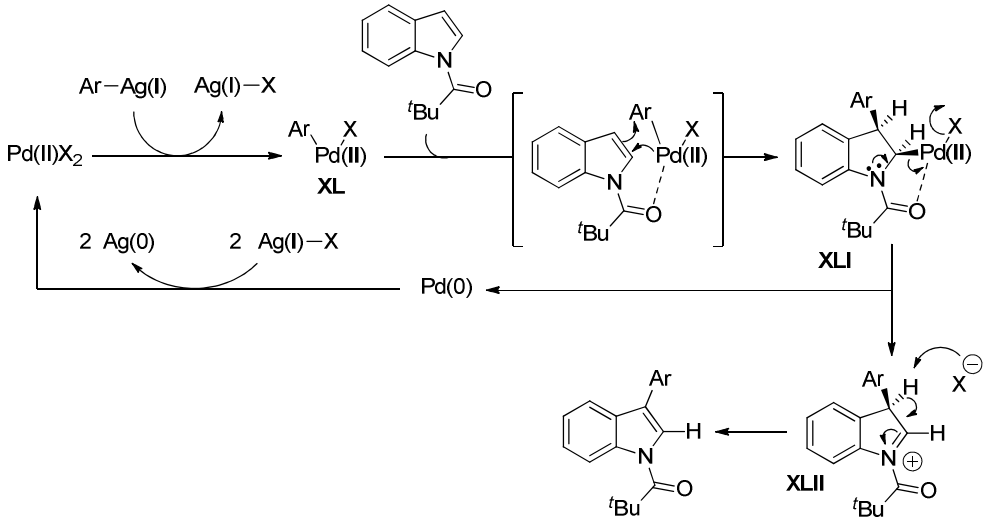
Scheme 68. Su's mechanism for the decarboxylative direct C–H arylation of indoles with benzoic acids.

Two possible pathways are proposed for this transformation. Path A involves the decarboxylation of the electron-donating benzoic acids. In this case, the decarboxylation occurs under catalysis of Pd(II) to generate the aryl-Pd(II) **XXXV**. Subsequently, the indole would then undergo electrophilic palladation at the C3 position to give **XXXVI** followed by migration to the C2 position.[49b] Reductive elimination would lead to the desired C2 coupled product with concomitant formation of Pd(0) which is then reoxidised back to Pd(II) by the Ag(I). Alternatively, when the carboxylic acid bears electron-withdrawing groups, path B is active. In the first step, the Ag(I) decarboxylates the acid generating the aryl-Ag(I). At this point, the aryl-Ag(I) transmetalates with **XXXVII** to give the indolyl-Pd(II) **XXXIX** through the transition state **XXXVIII**. The proposed transition state **XXXVIII** involves the coordination of the iminium ion to the Ag center thus fixing the conformation and resulting in the formation of the C3 regioisomer.[58]

In agreement with Su's results, we demonstrated that Ag(I) salts are responsible for the decarboxylation of the electron-withdrawing benzoic acids. Regarding the

activation of the indole on the other hand, other possible mechanisms could be envisaged as outlined here.

Initially, as shown in Scheme 59, it was proposed that a direct electrophilic aromatic palladation takes place at the C3 position of the indole. Nevertheless, there is a the tendency for Pd(II) to migrate from C3 to C2, as observed in a number of C2 direct indole arylation methodologies.[49] Taking this into consideration, a modified mechanistic proposal is outlined in Scheme 69.

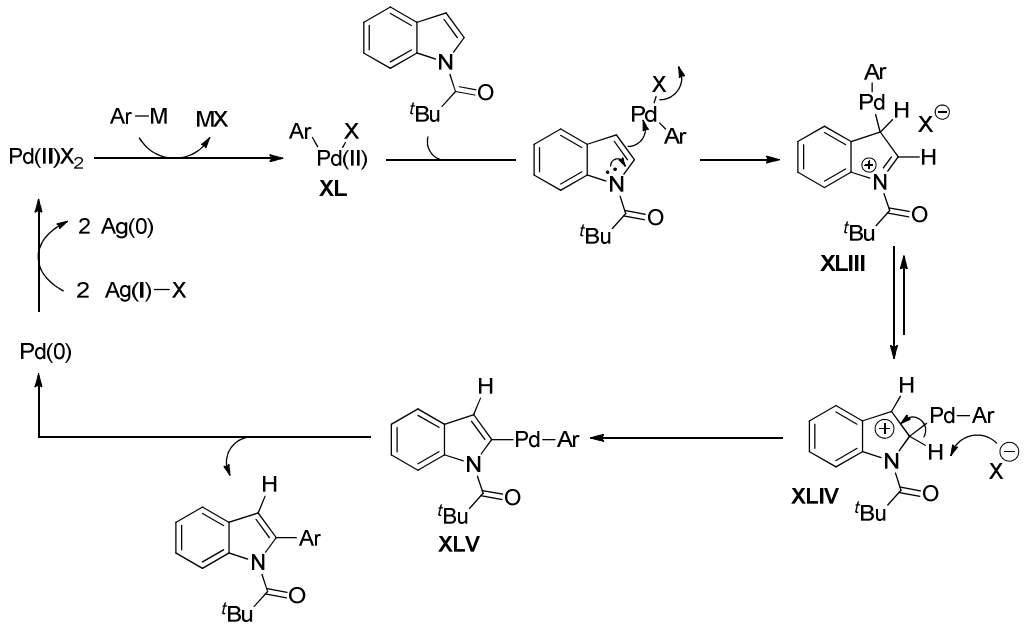


Scheme 69. Proposed mechanism for the observed regiochemistry in the decarboxylative arylation of indoles with electron-poor benzoic acids.

While the decarboxylation cycle was clearly proceeding via aryl-Ag(I) intermediates (Scheme 59), it was then hypothesised that upon the transmetalation with Ag(I), the aryl-Pd(II) **XL** species was formed (Scheme 69). **XL** could then undergo carbopalladation with the *N*-pivaloylindole. The coordination of the Pd center with the carbonyl group of the pivaloyl group would force the carbopalladation to occur in a regioselective fashion at the C3 position thus forming intermediate **XLI**. Subsequently, the lone pair of the nitrogen could drive the formation of Pd(0) upon formation of the iminium species **XLII**. Rearomatisation carried by the counter-ion would lead to the final product.

On the other hand, Su's observation for C2 regioselectivity could be rationalised by the presence of a highly electron-rich aryl-Pd species with less tendency to coordinate

to the carbonyl protecting group and therefore, respecting the natural pattern of reactivity in indoles (Scheme 70).



Scheme 70. Possible mechanism for Su's C2 arylation of indoles with electron-rich benzoic acids.

In summary, several mechanisms were proposed for this specific transformation. However, a generally accepted mechanism for the direct C–H arylation of indoles with benzoic acids has yet to be fully elucidated.

2.9. Conclusions

This chapter describes the development of the first intermolecular decarboxylative direct C–H arylation methodology. This protocol allows the coupling between benzoic acids bearing an *ortho* electron-withdrawing substituent such as Cl, NO_2 or F with indoles to give the corresponding C3 arylated adducts (**13**, **15**, **21**, **22**, **23** and **24**). However, this transformation has limited scope regarding the *ortho* electron-withdrawing group. Moreover, non *ortho* substituted benzoic acids failed to react presenting an additional limitation for this protocol.

On the other hand, MeO, Br, Cl, Me or CO_2Me groups present at the indole core were tolerated (compounds **25** to **31**), showcasing a broad substrate compatibility regarding this coupling partner. It is noteworthy that this protocol proceeds at much lower temperatures when compared to the reports on decarboxylative C−H arylation by Crabtree and Glorius.[31,32]

It is believed that this transformation proceeds via a Pd/Ag bimetallic system where the Ag(I) salt is not only acting as the oxidant but is also responsible for the decarboxylation of the benzoic acid. This transformation occurs with high regio- and chemo-selectivity, representing an excellent alternative to oxidative double C–H activation cross-couplings. In addition, low amounts of the coupling partner are required, in comparison to the large amounts needed in dehydrogenative cross-couplings.

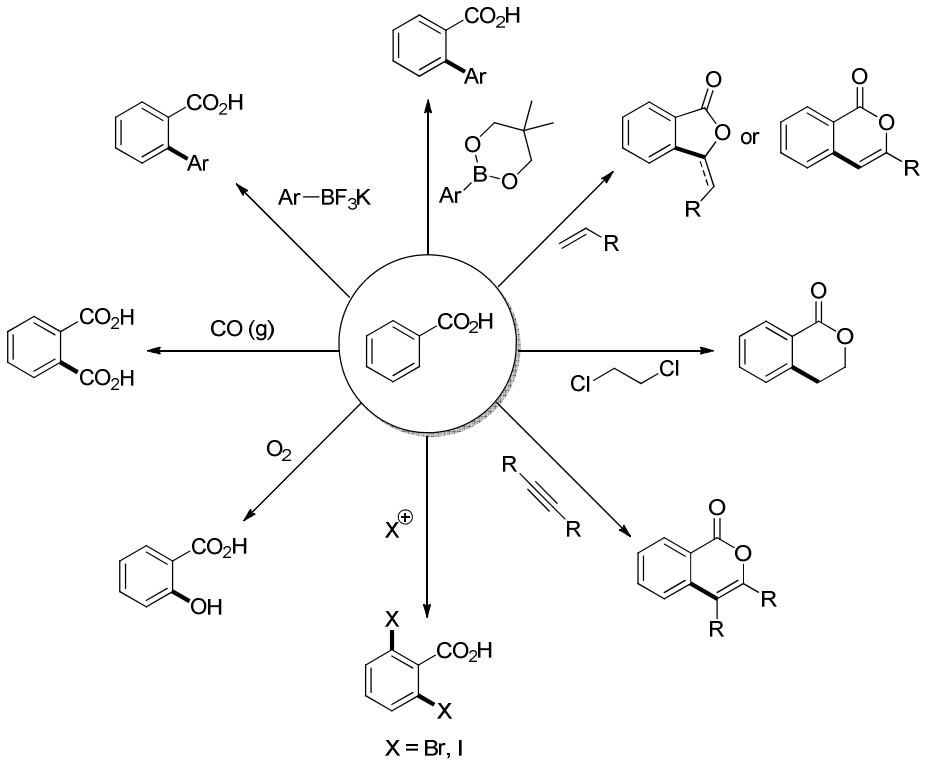
Despite the fact that decarboxylative C−H arylation methodologies have been demonstrated to be a perfect candidate for future cross-couplings, they are still far from competing with the current methods. Therefore, different challenges should be addressed in future work:

- The temperatures utilised in these transformations should be reduced to tolerate a wide range of sensitive groups. The aim of these transformations should be to develop a general room temperature decarboxylative C−H arylation protocol.
- A tremendous achievement towards greneer methodologies would be the use of O_2 as the terminal oxidant. The formation of CO_2 and H_2O as the byproducts would place decarboxylative methodologies amongst the greenest alternatives discovered to date.

Chapter 3. Ag(I)-catalysed protodecarboxylation of *ortho*-substituted benzoic acids[iii]

3.1. Introduction

The ability of carboxylic acids to direct the regioselectivity to their *ortho* positions in reactions of aromatic compounds has been widely exploited in organic synthesis. The potential of these substrates is illustrated in Scheme 71.



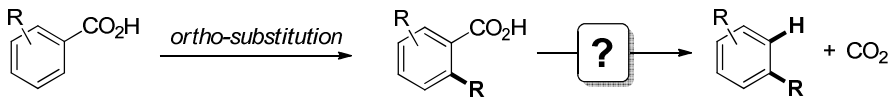
Scheme 71. Direct C−H functionalisation of benzoic acids.

For example, benzoic acids can guide the formation of C−C bonds using aryl donors such as boronic esters or aryltrifluoroborate salts (Molander salts) to produce *ortho* arylated benzoic acids.[59] In the same vein, they can react with, alkynes,[60] alkenes[61] or

[iii] Part of this work was done in collaboration with David Banawa (summer student) and Dr Carolina Sanchez (visiting PhD student, Universitat de Barcelona).

simple alkanes [62] to produce coumarin derivatives. Formation of salicylic acid derivatives or dicarboxylic acids was achieved by reacting benzoic acids with O_2 or CO respectively.[63] Benzoic acids can also be halogenated in *ortho* positions to form carbon−halogen bonds which can undergo further transformations.[64] In summary, benzoic acids have been demonstrated to serve as perfect directing groups for a plethora of synthetically useful transformations.

However, the utility of these transformations is limited when the target molecule does not bear the carboxylic acid group or a suitable derivative. Consequently, the development of methodologies for the removal of a carboxylic acid from the aromatic framework has received much attention in the past few years (Scheme 72).



Scheme 72. Protodecarboxylation of aromatic carboxylic acids.

The first studies on the metal-mediated protodecarboxylation of benzoic acids had limited scope, involved harsh conditions (>200 ºC) and the use of stoichiometric amounts of Cu(I) or Hg(II) salts.[7,8,9,10,65] As mentioned in chapter 1, Goossen and co-workers reported a catalytic version of this reaction using a Cu_2O/phenanthroline/quinoline system with a broad scope, albeit with the requirement for high reaction temperatures (160–190 ºC).[11] Subsequently, a Pd-catalysed decarboxylation of *ortho*-dimethoxy-substituted benzoic acids was also reported, although it requires high catalyst loadings (20 mol %) of $Pd(TFA)_2$ and the use of trifluoroacetic acid (10 equiv) as a co-solvent.[13] A mild and general methodology for the protodecarboxylation of benzoic acids is therefore still greatly needed.

3.2. Aim of the project

During our work on the use of bimetallic Pd/Ag systems for the direct C–H arylation of indoles in the presence of benzoic acids (see chapter 2), protodecarboxylation of the latter was observed as a byproduct. When investigating this side reaction, it was found that Ag(I) salts were capable of decarboxylating acids at 110 ºC. At this stage, it was hypothesised that a general method for the decarboxylation of benzoic acids could potentially be developed, mediated by Ag(I) salts. Precedent for a Ag-promoted protodecarboxylation has been previously reported.[66] However, this procedure involved high temperatures (240 ºC) and the use of stoichiometric amounts of Ag(I) salt. Based on our observations, it was envisaged that a protocol for the mild protodecarboxylation of benzoic acids mediated by Ag(I) salts could be developed.

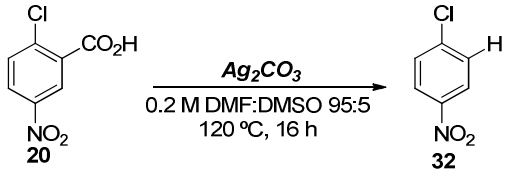
3.3. Optimisation of the reaction conditions

Initially, the protodecarboxylation of 2-chloro-5-nitrobenzoic acid (**20**) to **32** was investigated. At the onset, the initial conditions chosen were very similar to the conditions for the direct C–H arylation of indoles described in chapter 2 (Scheme 73).

Scheme 73. Ag(I)-mediated protodecarboxylation of **20.**

As depicted in Scheme 73, when **20** was treated with 3.0 equiv of Ag_2CO_3, complete conversion to **32**, at 120 ºC in a mixture of DMF:DMSO 95:5 was observed.

Gratifyingly, on reducing the amount of Ag(I), the reaction was found to be catalytic. The results are outlined in Table 10.

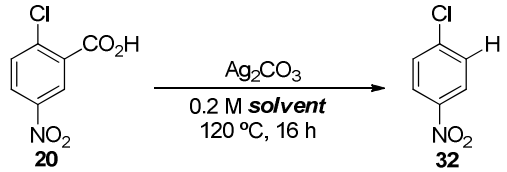


Entry	Ag_2CO_3	Yield of 32[a]
1	150 mol %	100%
2	10 mol %	98%
3	5 mol %	31%
4	1 mol %	9%

Table 10. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

It is important to mention that when the reaction is not quantitative, the remainder of the material is recovered as unreacted benzoic acid in all cases.

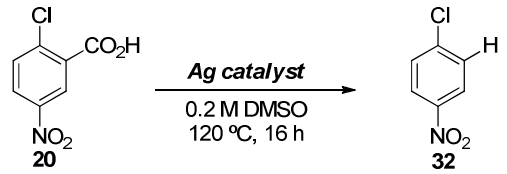
Subsequently, a solvent screening was carried out in the presence of 5 mol % of Ag_2CO_3. Different solvents were tested and, as shown in Table 11, negligible product formation was detected when toluene, H_2O, AcOH or 1,4-dioxane were employed (entries 1 to 4). On the other hand, when the reaction was carried out in DMF, 27% of the desired product **32** was obtained (entry 5). DMSO was found to be the optimal solvent for this particular reaction affording 57% of product (entry 6). It is noteworthy that 5 mol % of Ag_2CO_3 afforded quantitative yield of **32** in DMSO, although higher reaction temperatures were required (entry 7, 140 ºC). As depicted in entry 8, when 10 mol % of Ag_2CO_3 is used instead, complete conversion to **32** was obtained.



Entry	Ag_2CO_3	Tempertaure (ºC)	Solvent	Yield of 32[a]
1	5 mol %	120	Toluene	<5%
2	5 mol %	120	H_2O	0%
3	5 mol %	120	AcOH	0%
4	5 mol %	120	1,4-Dioxane	0%
5	5 mol %	120	DMF	27%
6	5 mol %	120	DMSO	57%
7	5 mol %	140	DMSO	100%
8	10 mol %	120	DMSO	100%

Table 11. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

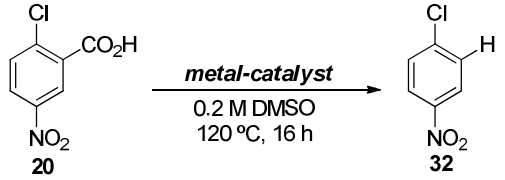
At this point, a range of Ag(I) salts were investigated. As shown in Table 12, good yields of **32** were obtained when a basic counterion on the Ag salt was used. Non-coordinating counterions such as TfO^- or BF_4^- did not afford any protodecarboxylated product.



Entry	Ag catalyst	Yield of 32[a]
1	10 mol % Ag_2O	80%
2	20 mol % AgOAc	85%
3	6 mol % Ag_3PO_4	79%
4	20 mol % AgTFA	22%
5	20 mol % AgOTf	0%
6	20 mol % $AgBF_4$	0%

Table 12. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

At this stage, other metal catalysts were tested to see whether they could mediate the decarboxylation process. The results are shown in Table 13.

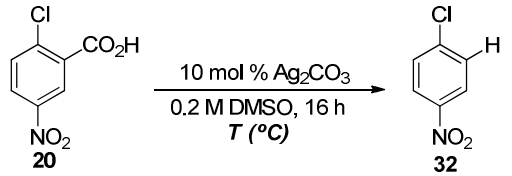


Entry	Metal-catalyst	Yield of 32[a]
1	20 mol % $Pd(TFA)_2$	0%
2	10 mol % Cu_2O	0%
3	10 mol % K_2CO_3	0%

Table 13. [a] Yields determined by NMR using mesitylene as an internal standard.

Other transition metals, such as Pd and Cu, known for their ability to decarboxylate benzoic acids, failed to react under the reaction conditions. In addition, the use of an alkali base such as K_2CO_3 did not afford the desired product **32**.

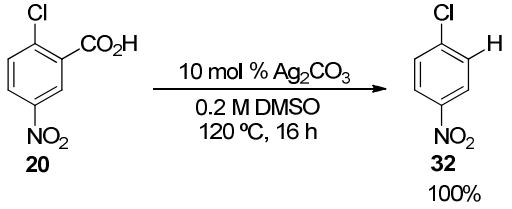
Different temperatures were also tested to find the mildest conditions for this protocol. As shown in Table 14, when the temperature was reduced to 110 ºC, the reaction was not quantitative, giving an 85% yield of **32**. Temperatures higher than 120 ºC still gave quantitative yields.



Entry	Temperature (°C)	Yield of 32[a]
1	110	85%
2	120	100%
3	140	100%

Table 14. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

In summary, the optimum conditions obtained for the protodecarboxylation of **20** are depicted in Scheme 74.

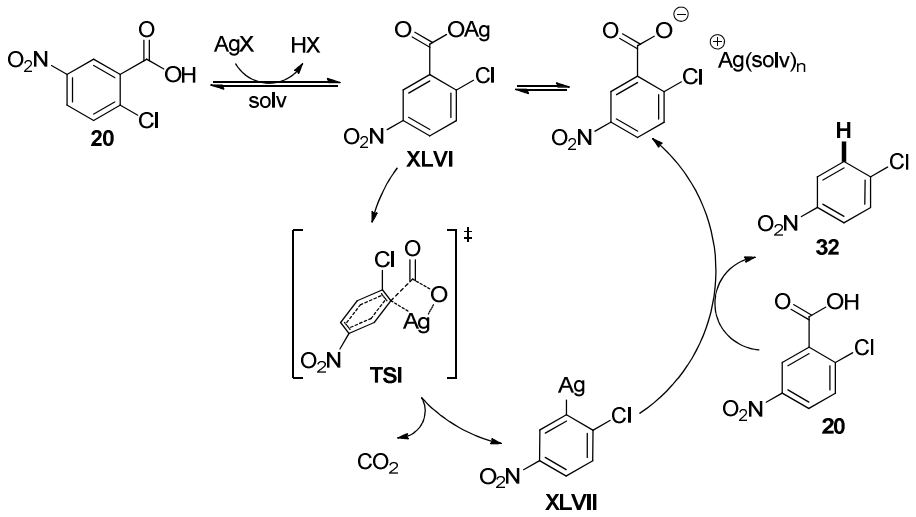


Scheme 74. Optimised conditions for the Ag(I)-catalysed protodecarboxylation of **20**

3.4. Proposed mechanism for the protodecarboxylation of 20

A plausible mechanism for the protodecarboxylation of **20** mediated by Ag(I) salts (AgX) is outlined in Scheme 75. An initial acid–base reaction of **20** with the Ag salt generates Ag carboxylate **XLVI**. In the case of weak coordinating counterion (X), the formation of the carboxylate is in equilibrium with a complete solvated Ag ion which could also be the active species involved in the decarboxylation step.. **XLVI** then undergoes decarboxylation through **TSI** to give aryl-Ag(I) **XLVII**. XLVII then reacts with **20** in an acid–base reaction, thus producing **32** and completing the catalytic cycle by regenerating Ag carboxylate **XLVI**. [iv]

[iv] The concerted mechanism for the decarboxylation (TSI) is speculative at this stage.



Scheme 75. Proposed mechanism for the Ag(I)-catalysed protodecarboxylation of **20.**

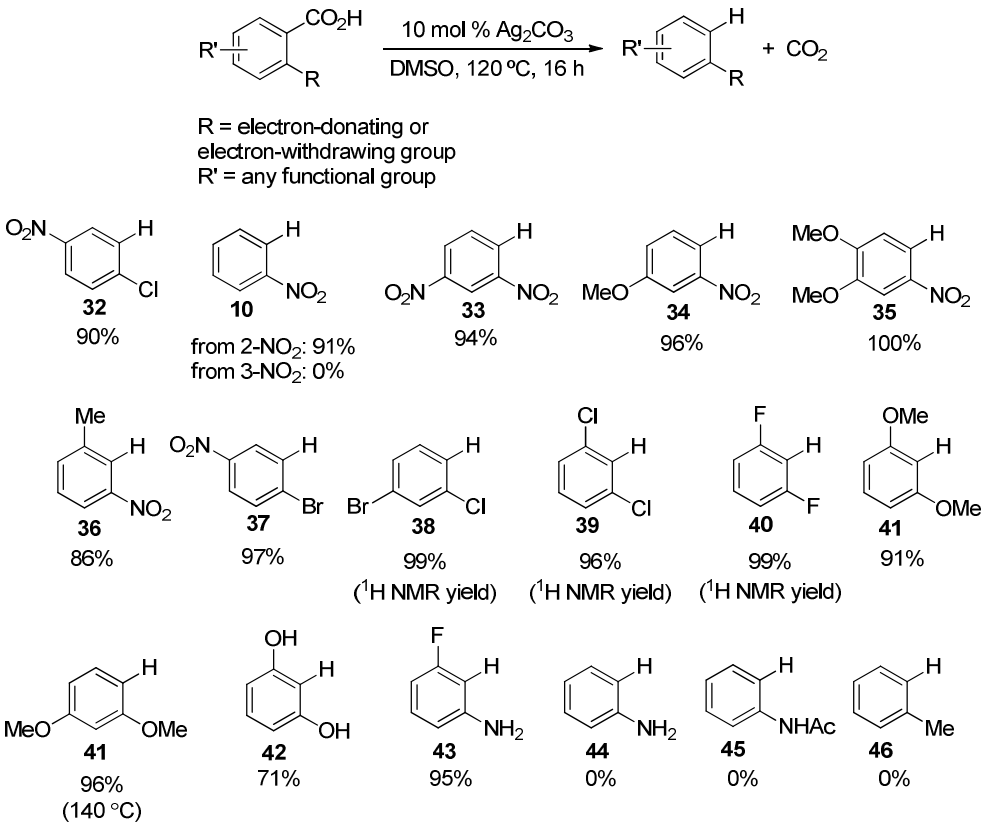
It is noteworthy that the proposed catalytic cycle depicted in Scheme 75 is similar to that proposed for the decarboxylation step in the decarboxylative C–H arylation of indoles described in chapter 2 (Scheme 59).

Recently, Su and co-workers have reported a theoretical study on the mechanism of the Ag-catalyzed decarboxylation of the benzoic acids.[67] In their work, they suggest that the need for an *ortho* substituent might be due to steric effects. The authors suggest that the presence of a bulky substituent at the *ortho* position produces an intrinsically steric effect and destabilises the starting carboxylate complexes thereby reducing the decarboxylation barrier. However, this explanation is not consistent with our observations, where the decarboxylation requires a strong electron-withdrawing group at the *ortho* position.

3.5. Substrate scope of the Ag(I)-catalysed protodecarboxylation protocol

The substrate scope of this new methodology was then examined. As shown in Scheme 76, a benzoic acid with an *ortho*-nitro group also led to an essentially quantitative yield of protodecarboxylation product **10**. The reaction also proved to be compatible with the inclusion of other electron-withdrawing and donating groups in

other positions of the ring (**33**, **34** and **35**), and even hindered doubly-*ortho*-substituted arene **36** afforded excellent yields of protodecarboxylation. It is noteworthy that positioning the nitro group in the *meta* position led exclusively to the recovery of unreacted starting material, indicating that an *ortho* substituent is necessary for the reaction to proceed. Gratifyingly, benzoic acids bearing other *ortho* electron-withdrawing groups, such as Br, Cl and F, including the hindered 2,6-dichlorobenzoic acid **39**, were found to easily undergo quantitative protodecarboxylation. In the case of **38**, **39** and **40**, it was found that the products were volatile and therefore, the yields in Scheme 76 are ^{1}H NMR yields using mesitylene as an internal standard.

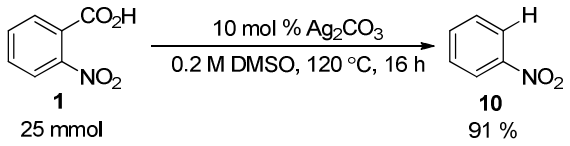


Scheme 76. Scope of the Ag(I)-catalysed protodecarboxylation of *ortho*-substituted benzoic acids. Yields of isolated pure material.

Interestingly, when the decarboxylation of benzoic acids substituted with the electron-

donating MeO group in an *ortho* position was attempted, the system also led to complete conversion to the protodecarboxylated product **41** (this product was obtained starting from 2,6-dimethoxybenzoic acid or 2,4-dimethoxybenzoic acid).[v] Remarkably, when unprotected hydroxyl groups were used, an excellent yield of corresponding arene **42** was also obtained without appreciable oxidation. Nitrogen-based electron-donating groups, such as free NH_2, were also found to be compatible with the reaction conditions (**43**), albeit not activating enough on their own (**44** and **45**). In addition, when a benzoic acid bearing a neutral group at the *ortho* position, such as *o*-toluic acid, was used, no protodecarboxylation product was observed (**46**).

This methodology is operationally simple. The reactions are not moisture or air sensitive and therefore do not require special precautions. After the reaction is complete, a simple aqueous work-up is used to eliminate any remaining traces of the starting material, affording analitically pure product after removal of the organic solvent, avoiding the necessity for column chromatography or distillation. To further demonstrate the potential of this methodology, protodecarboxylation of **1** on a 4.2 g (25 mmol) scale was performed. Pleasingly, 2.8 g of analytically pure **10** (91% yield) was obtained without any adjustment to the procedure (Scheme 77).



1
25 mmol

10
91 %

Scheme 77. Ag(I)-catalysed protodecarboxylation of **1** at 25 mmol scale.Yield of isolated pure material.

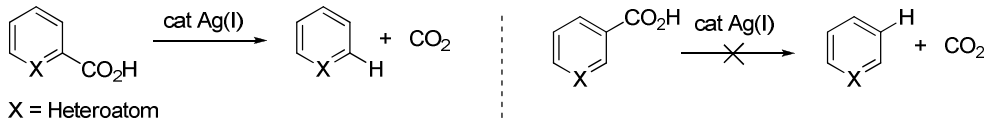
3.6. Exploration of the Ag(I)-catalysed protodecarboxylation protocol[vi]

As mentioned previously, one of the requirements for the protodecarboxylation of benzoic acids is the need for substitution at the *ortho* position regardless of whether this group is electron-donating or electron-withdrawing. During the exploration of the

[v] Protodecarboxylation of 2,4-dimethoxybenzoic to afford compound **41** acid was carried out at 140 ºC.

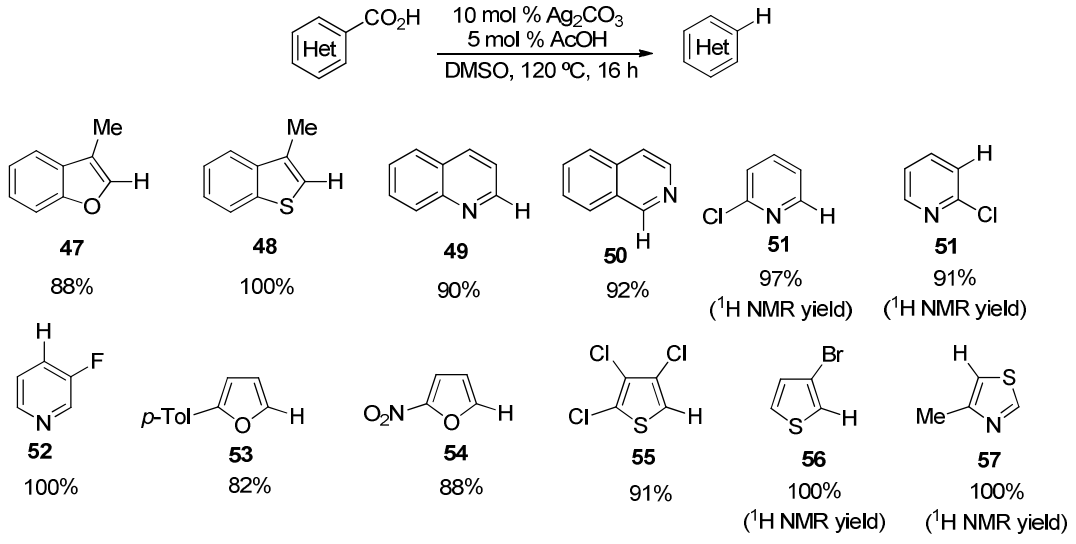
[vi] This work was developed in collaboration with Dr Pengfei Lu (PDRA, Queen Mary University of London) and Dr Carolina Sanchez (visiting PhD student, Universitat de Barcelona), and my main contribution was in a supervisory role.

protodecarboxylation of benzoic acids, it was discovered that heteroaromatic carboxylic acids bearing a heteroatom in the α position were also successfully protodecarboxylated. When this heteroatom was not α to the carboxylic acid, no protodecarboxylation was observed (Scheme 78). In summary, the carboxylic acid group that fulfills one of the two mentioned requirements would undergo Ag(I)-mediated decarboxylation.



Scheme 78. Ag(I)-catalysed protodecarboxylation of (hetero)aromatic carboxylic acids.

After a thorough optimisation, 10 mol % Ag_2CO_3 in combination with catalytic amounts of AcOH (5 mol %) at 120 ºC were determined to be the optimum conditions conditions for these substrates. As shown in Scheme 79, a wide range of different heterocycles, such as thiophenes, benzothiophenes, furans, benzofurans, quinolones, isoquinolines, pyridines or thiazoles, was obtained in excellent yields.

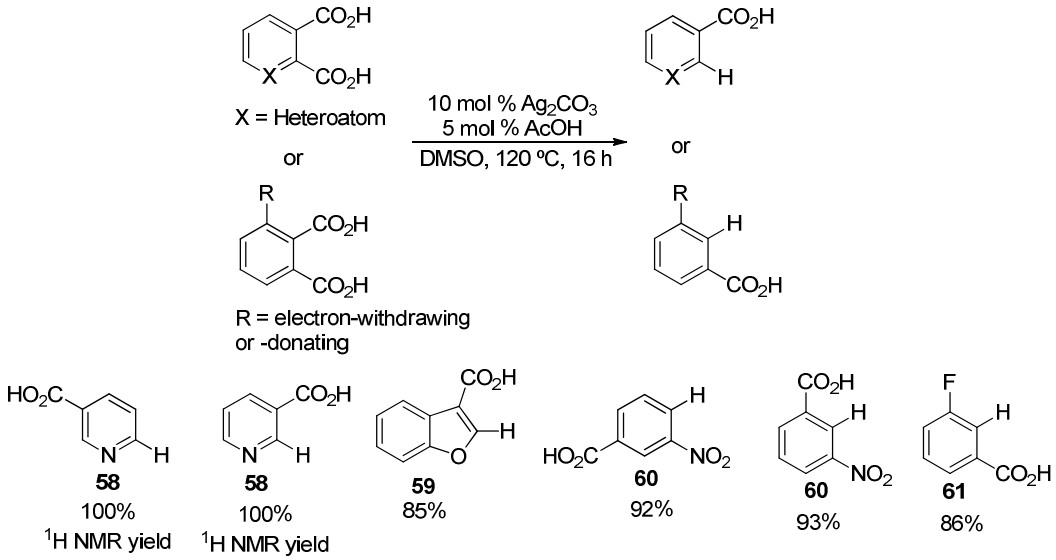


Scheme 79. Scope of the Ag(I)-catalysed protodecarboxylation of heteroaromatic acids. Yields of

isolated pure material.[vii]

When the heteroatom was not in α, but in ortho to an electron-withdrawing grup, the reaction smoothly afforded the decarboxylated product (Scheme 79, **51** and **52**). It is worth mentioning that products **51**, **52**, **56** and **57** were found to be volatile and the yield reported is determined by ^{1}H NMR analysis using mesitylene as internal standard.

On the basis of the remarkable activating effect of α heteroatoms and *ortho* electron-withdrawing groups, it was hypothesised that this methodology may be applied to the regioselective protodecarboxylation of aromatic compounds bearing more than one carboxylic acid. Indeed, when this protocol was applied to different dicarboxylic acids, complete regioselectivity was observed (Scheme 80). In every case, only the carboxylic acid α to a heteroatom or *ortho* to an appropriate substituent was removed, leaving the other carboxylic acid intact. It is noteworthy that adjacent carboxylic acid groups do not activate each other for protodecarboxylation.

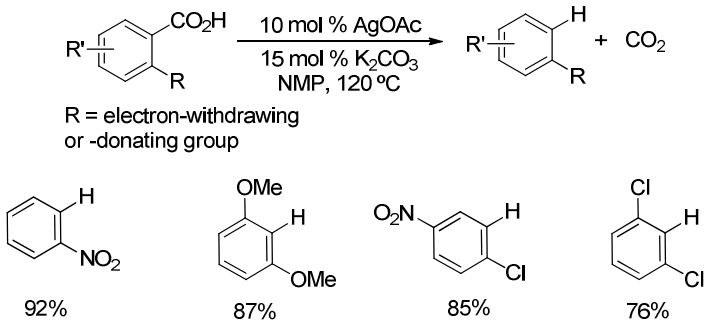


Scheme 80. Regioselective Ag(I)-catalysed protodecarboxylation of (hetero)aromatic carboxylic acids. Yields of isolated pure material.

[vii] Compound **51** was obtained without the presence of AcOH.

3.7. Concurrent work by other research groups

Concurrently with the work presented in this chapter, Goossen and co-workers developed a methodology for the decarboxylation of aromatic carboxylic acids.[68] Equally to our protocol, catalytic amounts of AgOAc and K_2CO_3 in NMP at 120 ºC allow the decarboxylation of a wide range of benzoic acids.



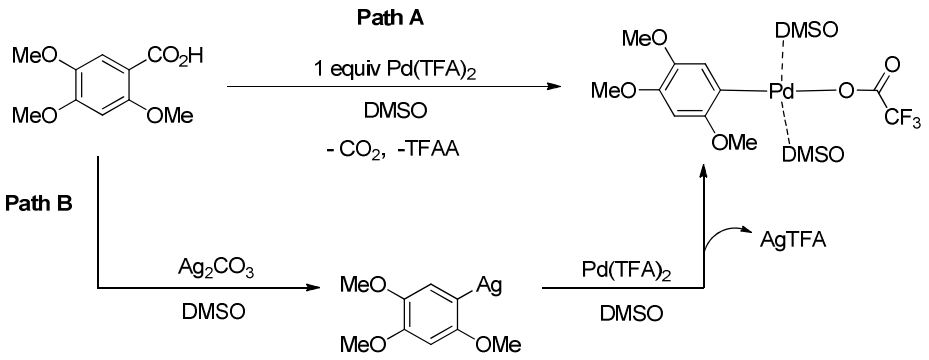
Scheme 81. Goossen's Ag(I)-catalysed protodecarboxylation of benzoic acids.

It is noteworthy that Goossen's protocol also requires an *ortho* substituent for the reaction to proceed. Analogous to our system, this substituent could either be an electron-withdrawing or an electron-donating group.

3.8. Implications of Ag(I)-catalsyed decarboxylation of benzoic acids on the mechanism of decarboxylative couplings

Several decarboxylative methodologies reported in the literature use Ag(I) salts on the reaction. In most of the reports the role of the Ag salt is believed to be the base or the oxidant. However, we have demonstrated in this chapter that Ag(I) salts are capable of decarboxylating aromatic benzoic acids. These findings imply a revision of the mechanism for the decarboxylation step in some of the decarboxylative methodologies reported.

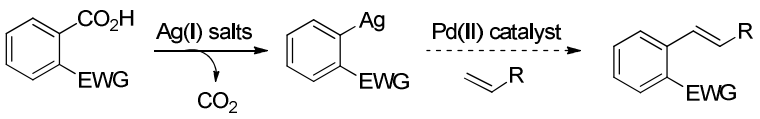
For example, in Myers' decarboxylative cross-coupling between benzoic acids and alkenes,[12,33] the authors suggest a Pd-mediated decarboxylation of the benzoic acid (chapter 1, Scheme 29). However, the mechanistic studies performed in those reports are limited to one class of benzoic acid (2,4,5-trimethoxy benzoic acid) (path A, Scheme 82).



Scheme 82. Decarboxylation of 2,4,5-trimethoxybenzoic acid.

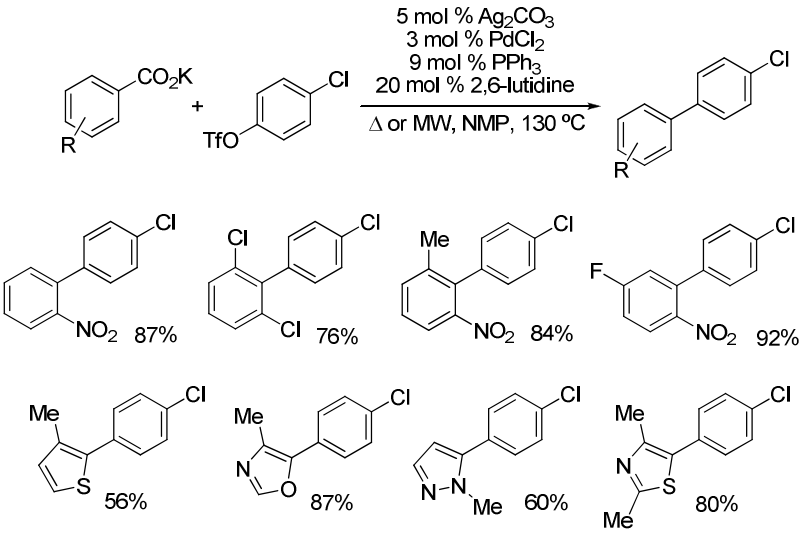
However, since benzoic acids bearing *ortho* electron-donating groups could also undergo decarboxylation under the presence of Ag(I) salts, another pathway for this transformation could be envisaged (path B, Scheme 82). Therefore, the Ag could also decarboxylate the benzoic acid which upon transmetalation with the Pd catalyst would afford the desired aryl-Pd species.

In addition, in their protocol benzoic acids bearing electron-withdrawing groups in the *ortho* position also undergo cross-coupling. We have demonstrated that Pd(II) salts are not able to mediate the decarboxylation of such benzoic acids. Therefore, we postulate that these particular acids do not undergo decarboxylation via a Pd(II) salt but via Ag(I), thus forming the aryl-Ag complex which undergoes transmetalation with the Pd catalyst and subsequent reaction with the double bond (Scheme 83).



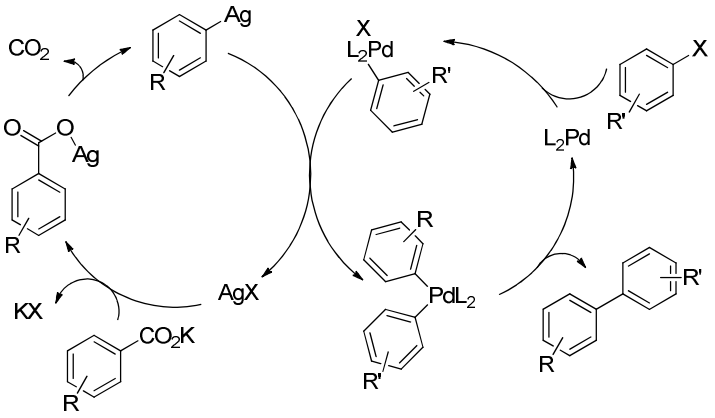
Scheme 83. Ag(I)-mediated decarboxylation of benzoic acids bearing *ortho* electron-withdrawing groups.

An example that supports this hypothesis is Goossen's decarboxylative arylation with aryltrifaltes. In their work, the authors report a catalytic Pd/Ag system which allows decarboxylative coupling catalytic *in both* Pd and Ag (Scheme 84).[69]



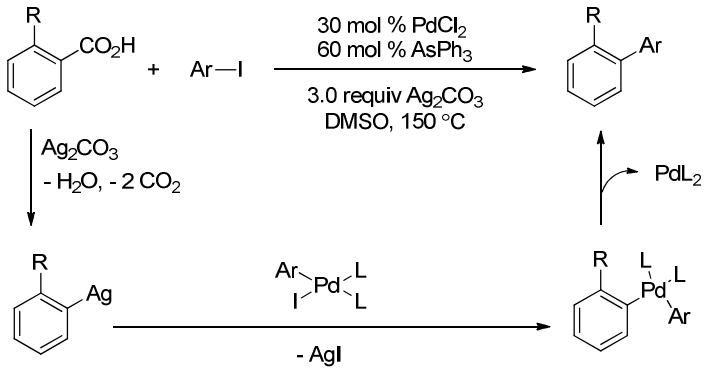
Scheme 84. Pd/Ag-catalyzed decarboxylative biaryl synthesis.

A wide variety of benzoic acids bearing *ortho* electron-withdrawing groups were successfully coupled with aryltriflates. Moreover, heteroaromatic carboxylic acids bearing a α heteroatom were also coupled in this transformation, suggesting that Ag is mediating the decarboxylation step. Indeed, the mechanism proposed is based on a double catalytic cycle (Scheme 85).



Scheme 85. Pd/Ag-catalysed decarboxylative arylation of benzoic acids.

Another example is the decarboxylative arylation described by Becht, Wenger and co-workers. In their work, the arylation of benzoic acids bearing *ortho* electron-withdrawing and –donating groups based on a Pd/Ag system is reported (Scheme 15).[21] However, no comments about the mechanism were described. Therefore, since the reaction allows the decarboxylation of these types of benzoic acids, we propose that Ag could be responsible for the decarboxylation of such benzoic acids (Scheme 86).



Scheme 86. Proposed Ag(I)-mediated decarboxylation in Becht and Wenger's protocol.

3.9. Conclusions

In this chapter a mild and simple methodology for the protodecarboxylation of benzoic acids bearing *ortho* electron-withdrawing (NO_2, Cl, Br, F) and electron-donating (OMe) is presented. This protocol proceeds at much lower temperatures than the previous protocols that use Cu,[11] and has a broader substrate scope than Pd-mediated decarboxylations.[13] Moreover, this methodology is compatible with sensitive functional groups such as unprotected phenols and amines. Although the exact reasons for an *ortho*-substituent being required are still under examination, they are most likely to be electronic. Further to the Ag(I)-catalysed protodecarboxylation of benzoic acids, an expansion of this protocol to the protodecarboxylation of a range of heteroaromatic carboxylic acids has been demonstrated. For heteroaromatic carboxylic acids the presence of a heteroatom in α to the carboxylic acid moiety is essential for the reaction to proceed. Furthermore, the need for either an *ortho*

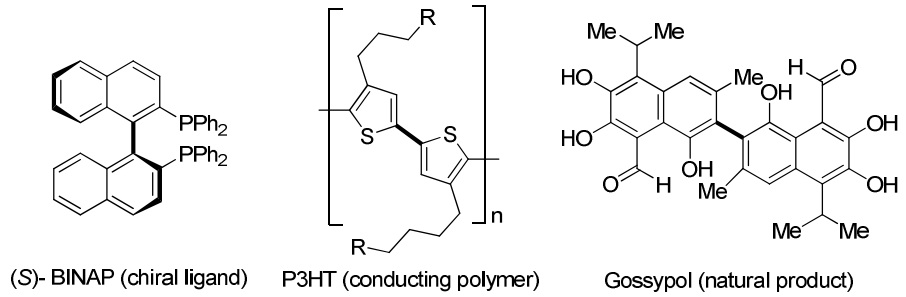
substituent or α heteroatom allowed us to develop a regioselective protodecarboxylation protocol where selective mono-protodecarboxylation products were obtained in excellent yields.

The fact that Ag salts have been shown to mediate decarboxylation has led us to reconsider some of the mechanisms reported in the literature concerning decarboxylative cross-couplings which make the use of Ag salts. In this regard, a discussion about the possibility on Ag-mediated decarboxylation has been analysed in a couple of illustrative examples.

Chapter 4. Decarboxylative homocoupling of (hetero)aromatic carboxylic acids[viii]

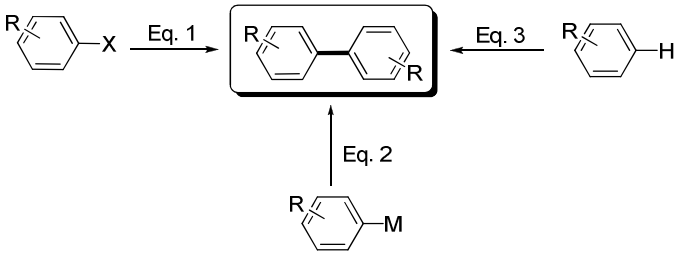
4.1. Introduction

Substituted symmetrical biaryl subunits constitute an important motif in chiral ligands,[70] monomers for conductive polymers,[71] natural products,[72] pharmaceuticals and pesticides (Scheme 87). [73]



Scheme 87. Examples of molecules bearing symmetric biaryls as part of their structure.

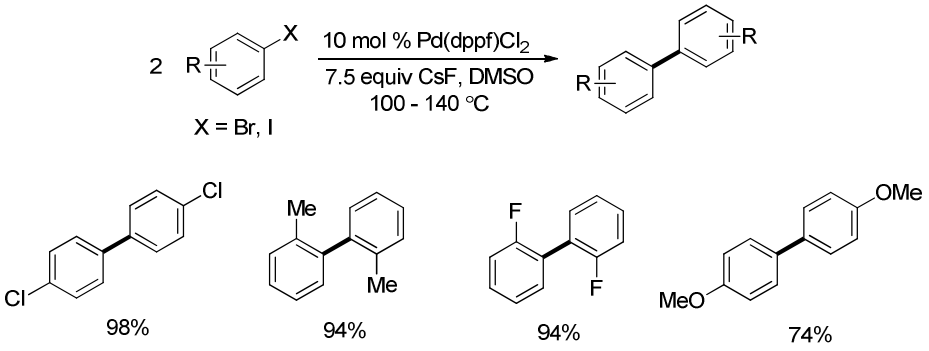
These structures are traditionally synthesised via the transition metal-mediated cross-coupling of suitably functionalised arene precursors, usually haloarenes or organometallic compounds (Scheme 88, Eq. 1 and 2).[74,75]



Scheme 88. Different approaches for the formation of symmetric biaryls.

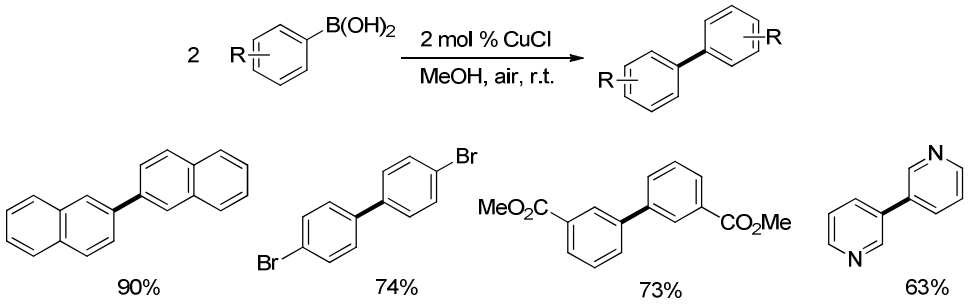
[viii] This work was done in collaboration with Hicham Lahlali (visiting student, ESCOM, France). Most of the experiments were designed by me and carried out by Hicham, under my direct supervision. I also analysed all the NMR, GCMS and other results and collected the information for the characterisation described in the experimental section, and drafted the manuscript for publication.

For example, Zhang, Qi and co-workers have recently reported a Pd-catalysed homocoupling of bromo- and iodoarenes in the presence of CsF (Scheme 89).[74c]



Scheme 89. Pd-catalysed homocoupling of aryl bromides and iodides.

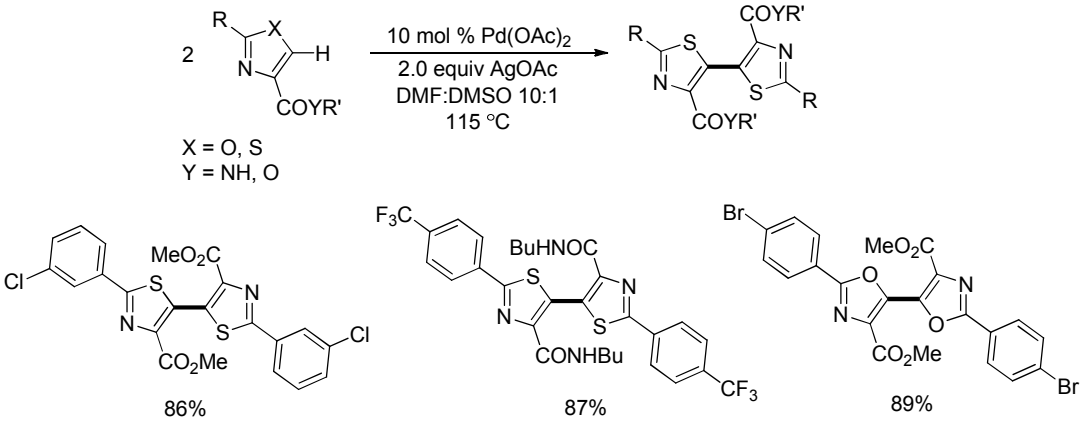
An example of the homocoupling of arenes using organometallic precursors is the oxidative Cu-catalysed homocoupling of arylboronic acids reported by Luo and co-workers. A combination of CuCl and MeOH at room temperature affords excellent yields of the symmetric biaryls (Scheme 90).[75e]



Scheme 90. Cu-Catalysed homocoupling of arylboronic acids.

As mentioned in previous chapters, the need for prefunctionalisation, together with the generation of undesired and often toxic by-products, are the main drawbacks for these approaches. Recently, a strategy involving the oxidative homocoupling of arenes via C–H bond activation has been shown to provide an alternative with increased atom and step economy (Scheme 87, Eq. 3).[76] Problems with the control of regio- and chemo-selectivity of C–H activation processes limit this approach to a

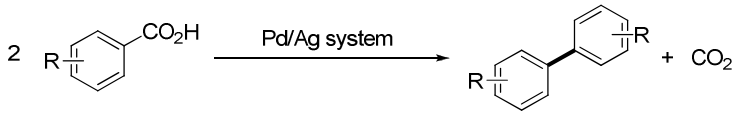
narrow range of arenes. An example of this approach is outlined in Scheme 90. Yao, Wu and co-workers developed an oxidative double C−H arylation protocol for the formation of symmetric heteroaryls (Scheme 91). This protocol proceeds with the use of $Pd(OAc)_2$ in combination of AgOAc in a mixture of DMF and DMSO.



Scheme 91. Pd-catalysed oxidative C−H homocoupling of thiazoles and oxazoles.

4.2. Aims of the project

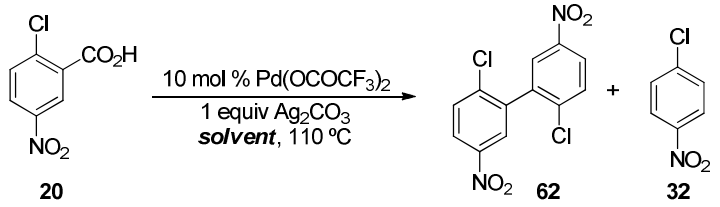
During the course of the previous work on the decarboxylative C–H arylation of indoles with benzoic acids (chapter 2), small amounts of the homocoupled product of the latter partner were observed. Consequently, the application of this protocol for the synthesis of symmetrical biaryls using a Pd/Ag system was envisaged. The control of the regioselectivity, the ready availability of (hetero)aromatic carboxylic acid starting materials and innocuous by-product formation (CO_2) allow this approach to be a useful strategy for this transformation, providing easy access to a variety of symmetric biaryls (Scheme 92).



Scheme 92. Decarboxylative approach for the formation of symmetric biaryls.

4.3. Optimisation of the decarboxylative homocoupling of (hetero)aromatic acids

Initially, the homocoupling of 2-chloro-5-nitro-benzoic acid **20** to afford biaryl **62** in the presence of 10 mol % $Pd(TFA)_2$ and Ag_2CO_3 at 110 ºC was investigated. In the beginning a screen of different solvents was carried out. The results are summarised in Table 15.

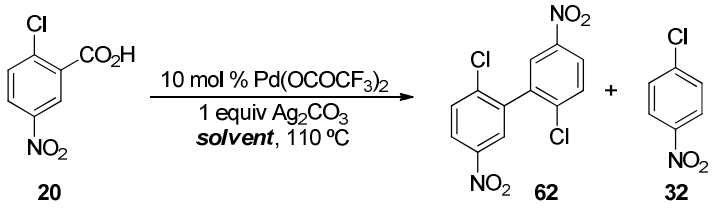


20 **62** **32**

Entry	Solvent	Yield 62[a]	Yield 32[a]
1	DMF	68%	18%
2	DMSO	58%	18%
3	DMA	46%	34%
4	1,4-Dioxane	0%	0%
5	NMP	0%	0%

Table 15. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

Gratifyingly, when highly polar solvents were used, the desired homocoupled product **62** was observed in reasonable yields (Table 15, entries 1, 2 and 3). Interestingly however, when NMP or 1,4-dioxane were tested, neither homocoupled product nor protodecarboxylation was observed and starting material was recovered. It is noteworthy that in entries 1, 2 and 3 the only observed by-product corresponded to the protodecarboxylation of **20**, leading to 4-chloronitrobenzene (**32**). In light of the good results obtained when DMF and DMSO were used as solvents, a combination of both solvents was tested. The results are outlined in Table 16.

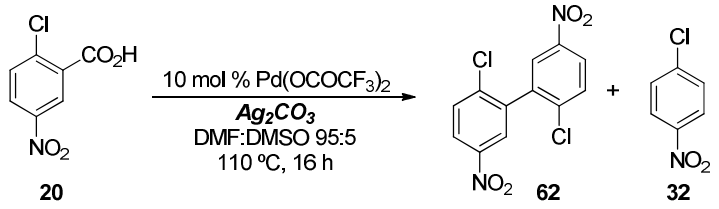


Entry	Solvent	Yield 62[a]	Yield 32[a]
1	DMF:DMSO (50:50)	75%	13%
2	DMF:DMSO (80:20)	76%	15%
3	DMF:DMSO (90:10)	77%	17%
4	DMF: DMSO (95:5)	76%	17%

Table 16. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

The use of DMF and DMSO as a solvent mixture proved to be successful, resulting in an increase of the yield of the coupled product **62** in about 10% yield (Table 16, entry 1). However, different combinations of such solvents did not affect the overall yield (Table 16, entries 2, 3 and 4). Consequently, DMF:DMSO 95:5 was determined to be the preferable ratio of solvent for further optimisation.

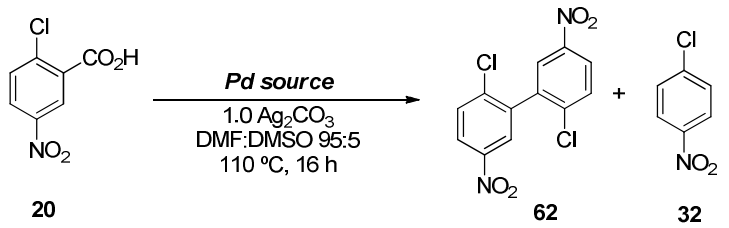
Optimisation of the amount of Ag_2CO_3 showed that an excess of this oxidant (1.0 equiv) was necessary to achieve high yields (Table 17, entry 3). Higher amounts of Ag_2CO_3 gave similar results, whereas 0.25 and 0.50 equiv reduced the yields considerably (Table 17, entries 1, 2 and 4, 5 respectively).



Entry	Ag_2CO_3	Yield 62[a]	Yield 32[a]
1	0.25 equiv	5%	48%
2	0.5 equiv	64%	32%
3	1.0 equiv	76%	19%
4	1.2 equiv	73%	14%
5	1.5 equiv	72%	18%

Table 17. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

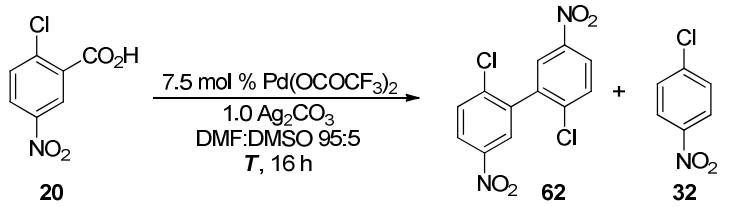
Optimisation of the Pd catalyst and its stoichiometry was then carried out. Phosphine-free Pd sources were found to give similar yields to $Pd(TFA)_2$ (Table 18, entries 1 and 2). On the other hand, bis-(triphenylphosphine)palladium dichloride complex (Table 18, entry 3) afforded substantially lower yields of **62** (37%). When different stoichiometries were tested, 7.5 mol % of $Pd(TFA)_2$ was determined to be the optimum catalyst loading, giving 79% yield of the homocoupling product **62** (Table 18).



Entry	Amount Pd source	Pd source	Yield 62[a]	Yield 32[a]
1	10 mol %	$Pd(OAc)_2$	73%	19%
2	10 mol %	$Pd(CH_3CN)_2Cl_2$	71%	13%
3	10 mol %	$Pd(PPh_3)_2Cl_2$	37%	58%
4	2.5 mol %	$Pd(OCOCF_3)_2$	68%	22%
5	5 mol %	$Pd(OCOCF_3)_2$	64%	23%
6	7.5 mol %	$Pd(OCOCF_3)_2$	79%	16%
7	15 mol %	$Pd(OCOCF_3)_2$	78%	16%

Table 18. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

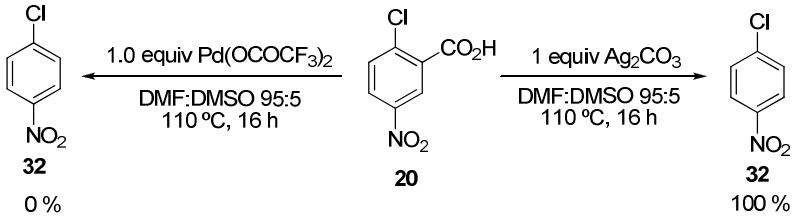
Finally, a screen of the temperature was carried out. As mentioned in chapters 2 and 3, an optimisation of the temperature is crucial in decarboxylative cross-couplings. The tandem nature of the two catalytic cycles requires a high degree of synchronisation where temperature is clearly a crucial parameter (*vide infra*). It was found that 120 ºC afforded **62** in 84% yield (Table 19, entry 3). Lower temperatures did not improve the yield of the desired product (Table 19, entry 1 and 2).



Entry	Temperature	Yield 62[a]	Yield 32[a]
1	100 °C	73%	23%
2	110 °C	79%	16%
3	120 °C	84%	13%

Table 19. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

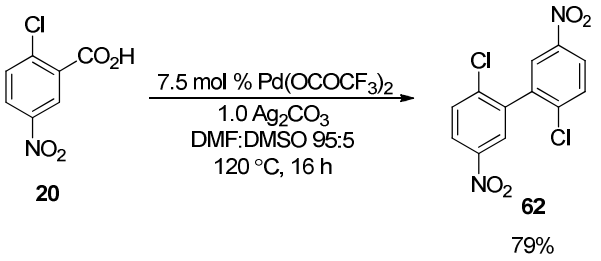
Analogous to the decarboxylative C–H arylation of indoles with benzoic acids, the absence of the Pd catalyst gave quantitative protodecarboxylation. However, when 1.0 equiv of $Pd(OCOCF_3)_2$ was used in the absence of Ag_2CO_3, no dimerisation was detected (Scheme 93). This demonstrates the need for both metals in the reaction, and that the Ag(I) salt is not just the terminal oxidant but also plays a role on the decarboxylation of the benzoic acid.



Scheme 93. Decarboxylation experiments in the presence of Pd or Ag.

To circumvent the formation of protodecarboxylated byproduct **32**, reactions were carried out in the presence of molecular sieves. However, this did not reduce the formation of **32**.

The optimised conditions for this decarboxylative homocoupling afforded biaryl **62** in 79% isolated yield (Scheme 94).

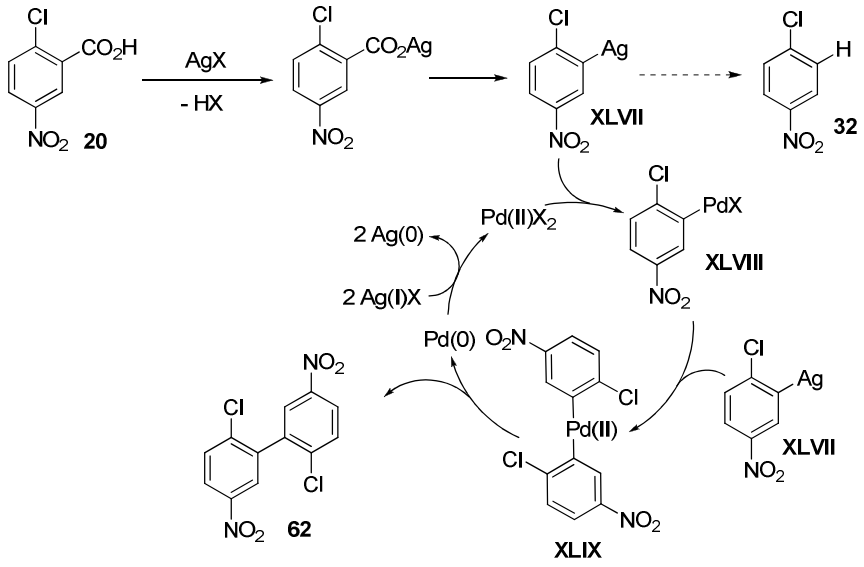


Scheme 94. Optimised conditions for the formation of **62**.

4.4. Proposed mechanism

A plausible mechanism for this transformation is outlined in Scheme 95. In chapter 3 it was demonstrated that Ag(I) salts can mediate the decarboxylation of *ortho* substituted benzoic and heteroaromatic acids. Therefore, the formation of aryl-Ag(I)

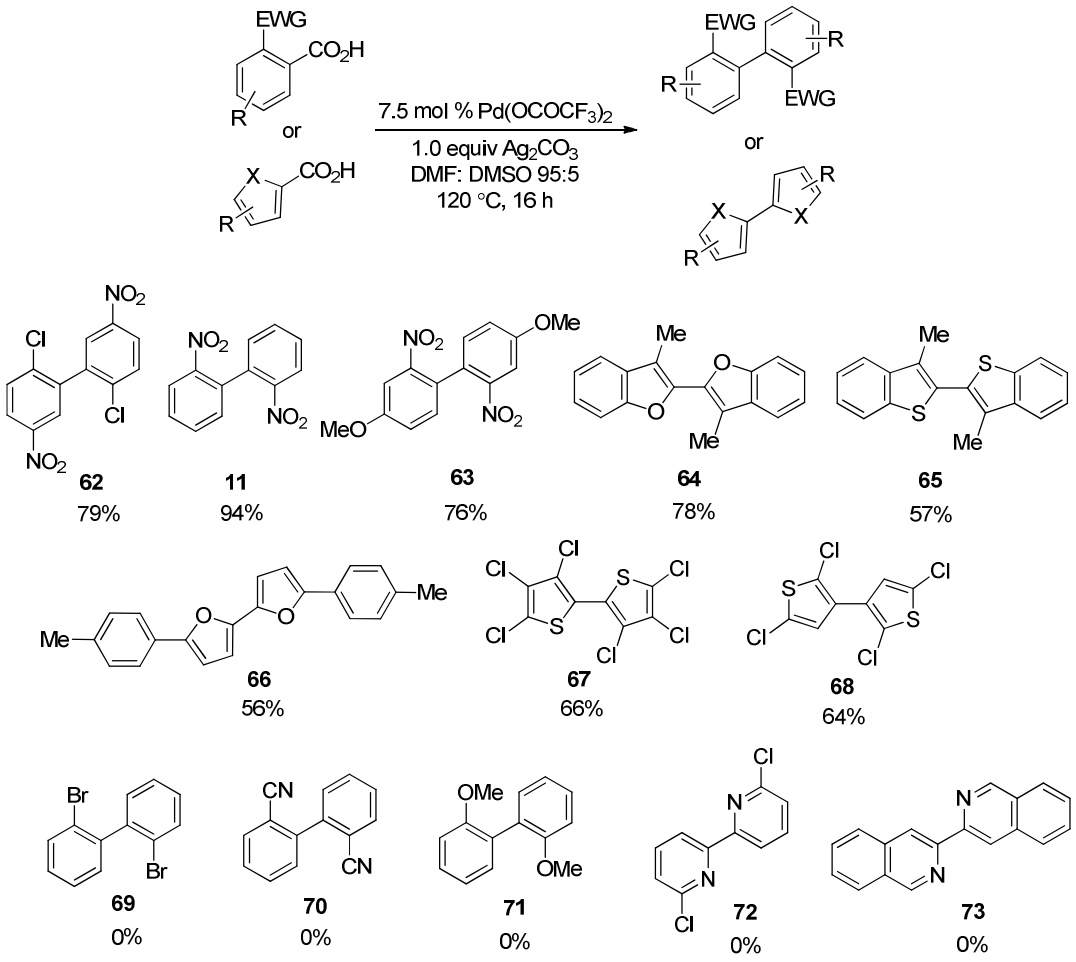
XLVII from benzoic acid **20** was envisaged as the initial step in the reaction. **XLVII** would then undergo transmetalation to Pd(II) affording intermediate **XLVIII**. A second transmetalation with another aryl-Ag(I), **XXLVII**, would generate bis-aryl-Pd species **XLIX**. Subsequent reductive elimination would then afford biaryl **62**. Finally, Ag(I) reoxidises Pd(0) to Pd(II), regenerating the catalyst. The observation of small amounts of protodecarboxylated product **32** is consistent with the formation of the aryl-Ag(I) which, as mentioned in chapter 2 and 3, has been reported to be highly reactive towards protodemetalation.[52]



Scheme 95. Proposed mechanism for the decarboxylative homocoupling of benzoic acids.

4.5. Scope of the decarboxylative homocoupling of benzoic acids

With the optimised protocol in hand, the scope with respect to other aromatic carboxylic acids was investigated. The results are outlined in Scheme 96.



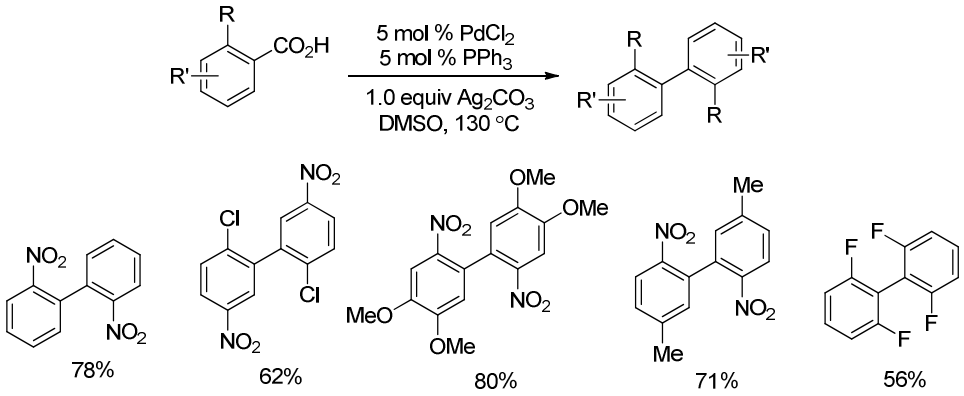
Scheme 96. Scope of the decarboxylative homocoupling of (hetero)aromatic carboxylic acids. Reaction for compounds **11**, **63** and **65** were carried out at 130 ºC. Yields of isolated pure material.

Various aromatic carboxylic acids were tested, and benzoic acids bearing *ortho* electron-withdrawing groups such as Cl or NO_2, underwent homocoupling to produce the desired biaryls **62**, **11** and **63** in excellent yields (Scheme 96). However, when other *ortho* electron-withdrawing groups, such as Br or CN were tested, the formation of dimer was not observed (**69** and **70**). Unfortunately, when the *ortho* substituent is an electron-donating group such as MeO, only protodecarboxylation of the parent carboxylic acid was observed (**71**). Pleasingly, oxygen and sulfur based heteroarenes, such as furans, benzofurans, benzothiophenes and thiophenes containing a carboxylic acid at C2, reacted smoothly under the reaction conditions to afford biaryls **64**-**67** in good to excellent yields. A thiophene bearing the acid functionality at C3 and an *ortho* Cl substituent also afforded good yields of the corresponding biaryl **72**. The

formation of protodecarboxylation as the byproduct suggests that the relative rates of protodemetallation of **XLVII** versus transmetalation to Pd are highly affected by the nature of the group at the *ortho* position (Scheme 95).

4.6. Recent examples of double decarboxylative arylation

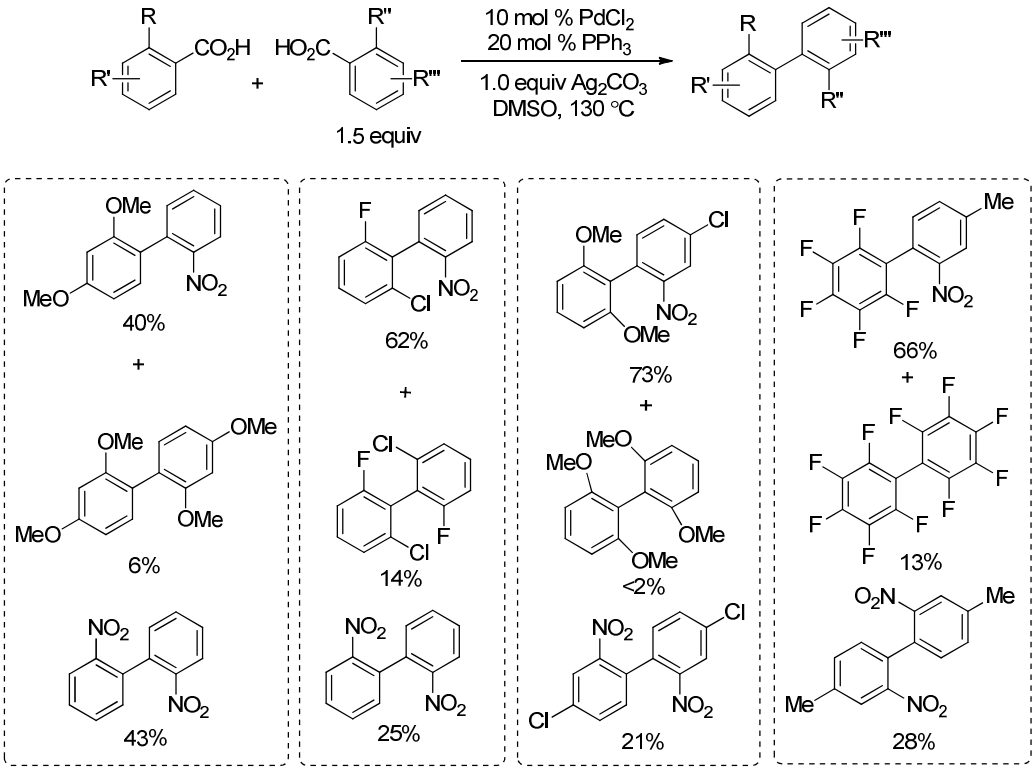
Tan, Deng and co-workers have recently developed a protocol for the homocoupling of benzoic acids,[77] where catalytic amounts of Pd were used in combination with PPh_3 and Ag_2CO_3. The results are outlined in Scheme 97.



Scheme 97. Tan and Deng's decarboxylative homocoupling of benzoic acids.

In this case, only electron-withdrawing groups such as Cl, NO_2 or F were tolerated in this system. However, no examples of heteroaromatic carboxylic acids were reported.

The authors also report the possibility of using the same reaction conditions for the formation of heterobiaryls (Scheme 98).



Scheme 98. Tan and Deng's decarboxylative heterocoupling of benzoic acids.

The strategy adopted by the authors combined electron-rich benzoic acids with electron-poor benzoic acids. Although some examples have been reported to give good yields of the heterocoupled product, others still suffer from the formation of large amounts of homocoupling byproduct. Despite the low selectivity obtained, this work demonstrates that oxidative double decarboxylative cross-couplings are possible and furthermore, they can clearly compete with oxidative double C−H arylation methodologies since no excess of coupling partner are required and the regioselectivity is completely controlled.

4.7. Conclusion

In this chapter, the first decarboxylative homocoupling of aromatic and heteroaromatic carboxylic acids is presented. This methodology allows the preparation of a variety of symmetric biaryls in good to excellent yields. However, similarly to the reactivity observed in chapter 2 and 3, only aromatic acids bearing

ortho electron-withdrawing or α heteroatoms were successfully coupled. It is shown that *ortho* Cl, and NO_2 groups afforded the biaryl structures in excellent yields (**11**, **62** and **63**). Symmetric heteroaromatic compounds were also obtained in good to excellent yields (**64** to **68**).

It is believed that this transformation proceeds via a Ag(I)-mediated decarboxylation of the aromatic carboxylic acid whereas the Pd is responsible for the coupling process.

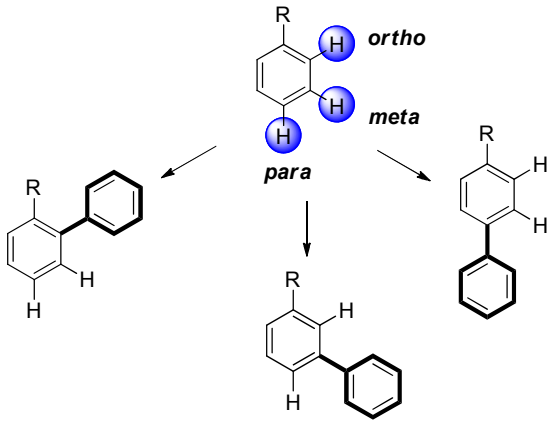
It is worth mentioning that to the best of our knowledge, this work is the first example of a double decarboxylative cross-coupling. Although this approach is in its early stages, several advantages could be envisaged:

- As mentioned in the introduction, this methodology would remedy the regioselective challenges present in the current oxidative double C−H arylation approaches.
- However, work must be done to address the applicability of this method to other aromatic acids. The need for an *ortho* electron-withdrawing group and a α heteroatom is one of the main limitations of this protocol.
- The use of O_2 as the terminal oxidant would provide a perfect alternative to the current methodologies, thereby producing CO_2 and H_2O as byproducts.
- Following up with Tan and Deng's work, the next goal for this approach would be its application for the generation of heterobiaryls. The objective would be to use two different carboxylic acids, which are coupled together, generating exclusively the heterobiaryl coupling product. Tan and Deng's protocol however,[77] does not result in a high level of heterobiaryl selectivity (Scheme 98). Therefore, further investigation into developing a protocol that is completely selective is still greatly needed.

Chapter 5. Carboxylic acids as traceless directing groups for formal *meta*-selective arylation

5.1. Introduction

Our research group has focused its investigations on the development of methods to avoid complex functional group manipulations through C–H bond functionalisation. A key aspect of this approach is the ability to control the site selectivity of these transformations. Due to the potential presence of numerous C−H bonds in an arene, the development of regioselective methods for direct arylation presents a challenge. For example, arylation in a monosubstituted arene could take place at the *ortho*, *meta* or *para* positions as depicted in Scheme 99.

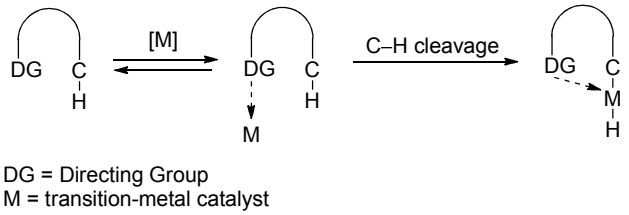


Scheme 99. Possible products of C−H arylation.

This regioselectivity problem has led synthetic chemists to undertake research into new strategies to solve this challenge. To this end, a number of regioselective C−H arylation methodologies have arisen in the past few years, exploiting the use of *directing groups* (DG).

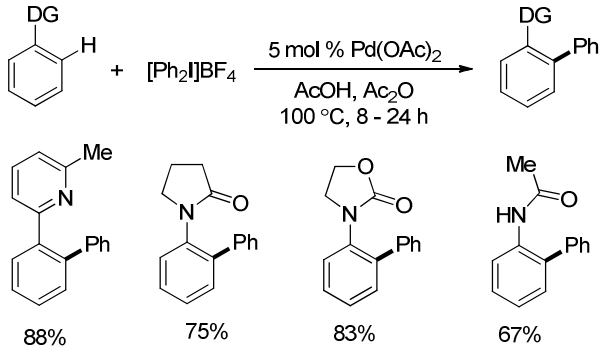
In this approach, a Lewis-basic directing group coordinates to the transition-metal

catalyst, which enables an intramolecular cleavage of the C−H bond[ix] (Scheme 100). This strategy allows intermolecular C−H arylations to be accomplished in a highly regioselective fashion.



Scheme 100. Regioselective C−H cleavage through the use of directing groups.

This particular strategy has given rise to a plethora of regioselective C−H transformations mainly for the *ortho* arylation of arenes.[42] For example, Sanford and co-workers developed a strategy for the regioselective arylation of arenes using 2-phenylpyridines, pyrrolidones, oxazolidinones and acetamides as effective directing groups.[78] The use of $Pd(OAc)_2$ and bis-aryl iodonium(III) species as coupling partners afforded complete regioselectivity at the *ortho* position (Scheme 101). In any case, regioselectivities other than *ortho* were not observed.

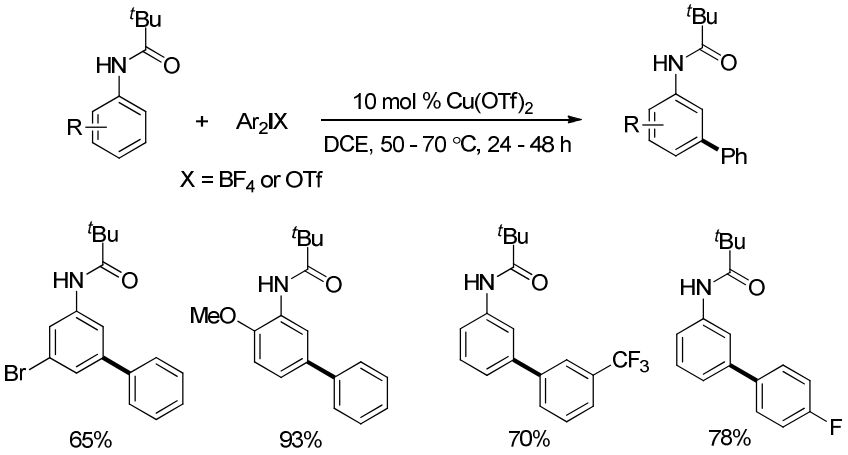


Scheme 101. Pd-catalysed direct C−H arylation of arenes using different directing groups.

Despite the apparent advantages of this strategy, the vast majority of these methodologies are still restricted to arylation to the *ortho* position.

[ix] This coordination must be reversible to allow turnover of the catalyst.

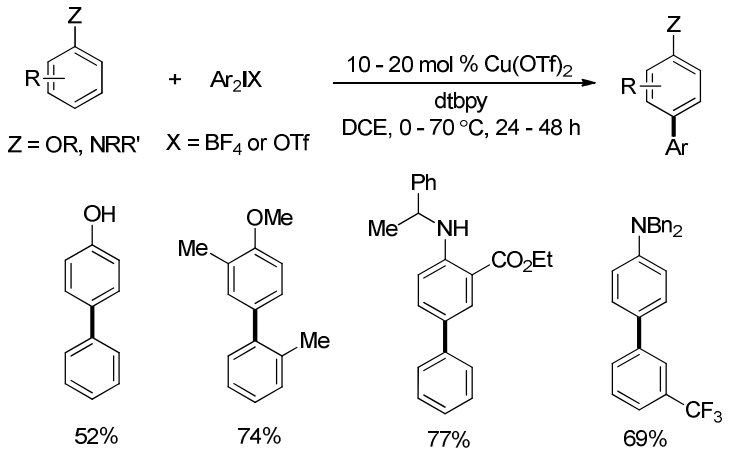
In contrast to the large contribution to *ortho* C−H arylation methodologies, methods for *meta*-selective direct C−H arylations are scarce. Recently, Gaunt and co-workers reported the first *meta* directed C−H arylation of arenes using pivalamides as directing groups.[79] The protocol proceeds under Cu catalysis and makes use of bis-aryl iodonium(III) species as coupling partners (Scheme 102). This work was further extended to the use of 2-oxo-substituted directing groups.[80]



Scheme 102. Cu-catalsyed *meta*-selective arylation of arenes with pivalamides as directing groups.

Despite the importance of this procedure, it still presents several limitations, namely the exclusivity to one type of directing groups, and the use of non-readily available bis-aryl iodonium(III) species.

Equally to *meta* directed C−H arylation, methodologies for *para*-selective arylation of arenes are also rare. Recently, Gaunt's research group has reported the arylation of phenols and anilines at the *para* position (Scheme 103).[81]

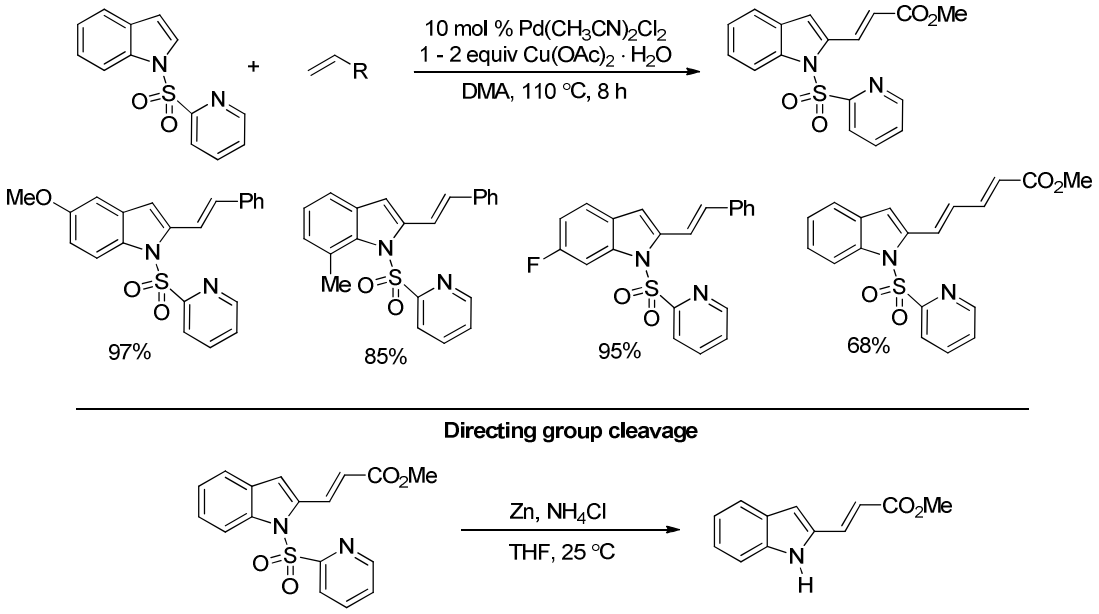


Scheme 103. Cu-catalysed *para*-arylation of phenols and anilines.

All of these strategies to control the regioselectivity of direct arylation rely on a limited number of directing groups. These require subsequent modification if a different substituent is required within the target molecule. On the contrary, the ideal direct arylation system would allow regioselective coupling, regardless of the nature of the substituents present on the arene.

Synthetic chemists have therefore focused their attention into the use of *removable directing groups* (RDG). This approach is based on the use of a directing group which can be efficiently removed after the site-selective reaction.[82]

Indeed, RDG have been investigated for direct functionalisation of C−H bonds, and Scheme 104 exemplifies the use of a 2-pyridylsulfonyl group as an efficient RDG for the direct C−H alkenylation of indoles, as reported by Carretero *et al*.[83]



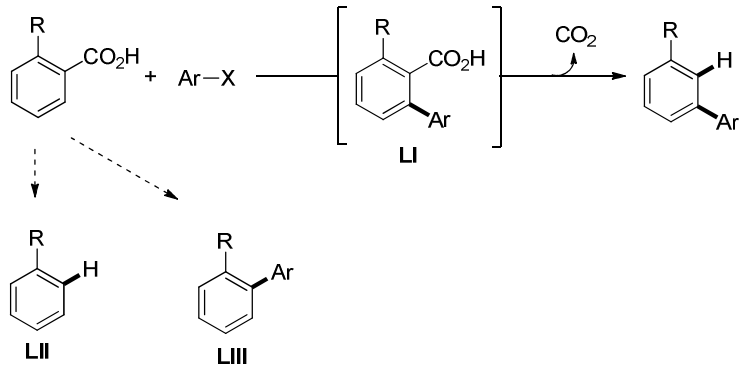
Scheme 104. C2-selective direct C−H alkenylation of indoles.

While the alkenylation proceeded exclusively at the C3 position for unprotected indole under these reaction conditions, the use of *N*-(2-pyridyl)sulfonyl afforded exclusively C2 alkenyl indoles. A simple cleavage of the protecting group using Zn/NH_4Cl at room temperature afforded the unprotected indole products.

5.2. Aim of the project

Our approach to overcoming the limitations of a *meta*-arylation relied on the possibility of using a strategically placed removable *ortho*-directing group. This is particularly important in the case of *meta*-selective arylations as, to date, only one class of directing group has been reported.[79]

Throughout this thesis it has been demonstrated that Ag(I) salts are able to efficiently decarboxylate benzoic acids bearing *ortho* elctron-withdrawing or -donating groups (chapter 2, 3 and 4). In another context, carboxylic acids are well known for being excellent directing groups for direct C−H *ortho* functionalisation (Scheme 71). Building upon these concepts, the formation of *meta*-substituted adducts by the use of carboxylic acids following the strategy postulated in Scheme 105 was envisaged.



Scheme 105. Benzoic acids as traceless directing groups for a formal *meta*-arylation.

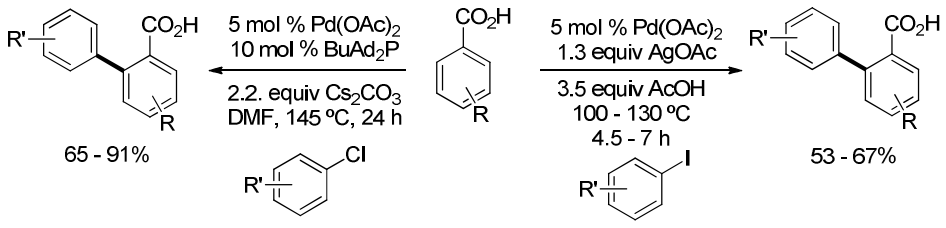
Unlike the great majority of methods using removable directing groups, the aim of this approach is to cleave the directing group (CO_2H) in situ, thus delivering exclusively the formal *meta*-arylated adduct without the need of further transformations. However, several challenges have to be addressed in this strategy:

- Can highly hindered substrates **LI** be protodecarboxylated?
- Can protodecarboxylation of the starting *ortho*-substituted benzoic acid, which would give **LII,** be prevented?
- Can the alternative decarboxylative *ipso*-arylation process observed in decarboxylative transformations (chapter 1), which would lead to *ortho*-substituted adducts **LIII**, be avoided?

5.3. Optimisation of the formal *meta*-arylation using benzoic acids[x]

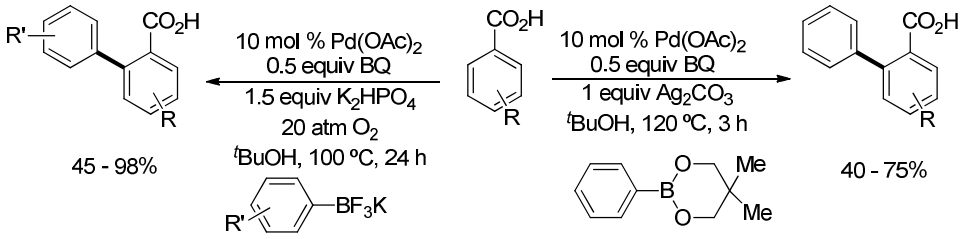
In 2007, Daugulis and co-workers developed a protocol for the *ortho*-arylation of benzoic acids.[84] Aryl chlorides and iodides were successfully coupled under Pd catalysis with Ag_2CO_3 in AcOH (Scheme 106).

[x] The initial optimisation process was carried out by Marika Righi (visiting PhD student, Universittá di Urbino).



Scheme 106. Direct *ortho*-arylation of benzoic acids.

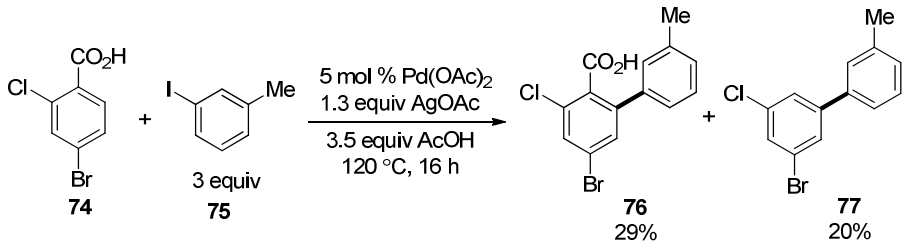
Similarly, Yu and co-workers developed an oxidative coupling for the arylation of benzoic acids at the *ortho*-position.[59] In these cases, arylboronic esters and potassium aryltrifluoroborates were used as coupling partners (Scheme 107).



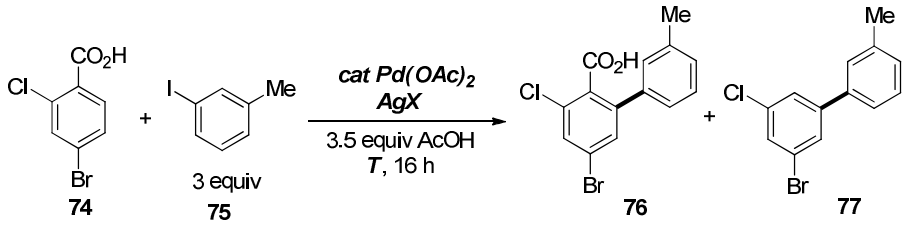
Scheme 107. Oxidative *ortho*-arylation of benzoic acids.

Based on these repots, we attempted the tandem arylation/decarboxylation strategy using *ortho*-substituted benzoic acids and iodoarenes as coupling partners.

At the onset, the reaction between 4-bromo-2-chlorobenzoic acid (**74**) and 3-iodotoluene (**75**) under Daugulis' conditions was attempted.[84] Disappointingly, only 29% of the *ortho*-arylated benzoic acid **76** was obtained (Scheme 108). However, upon further examination, a very encouraging 20% of the tandem arylation/protodecarboxylation **77** was also observed. This result indicated that the initially hypothesised tandem *ortho*-arylation/protodecarboxylation was feasible. Optimisation of this process was then carried out and a summary is outlined in Table 20.



Scheme 108. Arylation of **74** using aryl iodide **75**. Yields determined by ^{1}H NMR using mesitylene as internal standard.

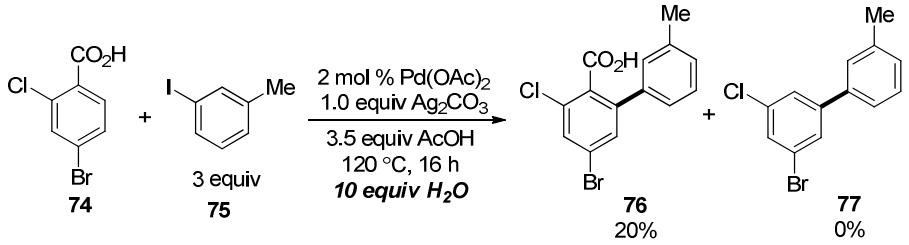


Entry	Pd mol %	AgX (equiv)	T (ºC)	Yield of 76	Yield of 77
1	10	AgOAc (2.0)	120	33%	28%
2	2	AgOAc (2.0)	120	17%	44%
3	1	AgOAc (2.0)	120	16%	41%
4	2	Ag_2CO_3 (1.0)	120	65%	9%
5	2	Ag_2CO_3 (1.0)	130	0%	73%

Table 20. Summary of the optimisation for the formal *meta*-selective C−H arylation of **74** with aryl iodide **75**. Yields determined by ^{1}H NMR using mesitylene as internal standard.

Optimisation of this reaction showed that lower catalyst loadings led to higher overall yield (**76** + **77**), with 2 mol % of $Pd(OAc)_2$ being the optimum (Table 20, entries 1-3). Replacing AgOAc with Ag_2CO_3 further increased the overall yield (**76** + **77**), although the protodecarboxylation step was greatly reduced (Table 20, entry 4). An increase on the temperature from 120 to 130 ºC allowed the tandem process to occur, producing exclusively the *meta*-arylated adduct **77** in 73% overall yield (Table 20, entry 6). It is noteworthy that the remainder of the material was recovered as unreacted starting material **74**. Under these reaction conditions the protodecarboxylation step seems to be chemoselective for **77** in the presence of **74** (a discussion on the origin of this chemoselectivity will be discussed in section 5.5).

It is noteworthy that aged Ag_2CO_3 significantly lowered the yield of **76** + **77**. This effect was attributed to the presence of variable amounts of water in the Ag salt. It was believed that water enhanced the protodecarboxylation rate in the benzoic acid starting material **74**. To verify this hypothesis, the reaction was carried out in the presence of 10 equiv of H_2O (Scheme 109).

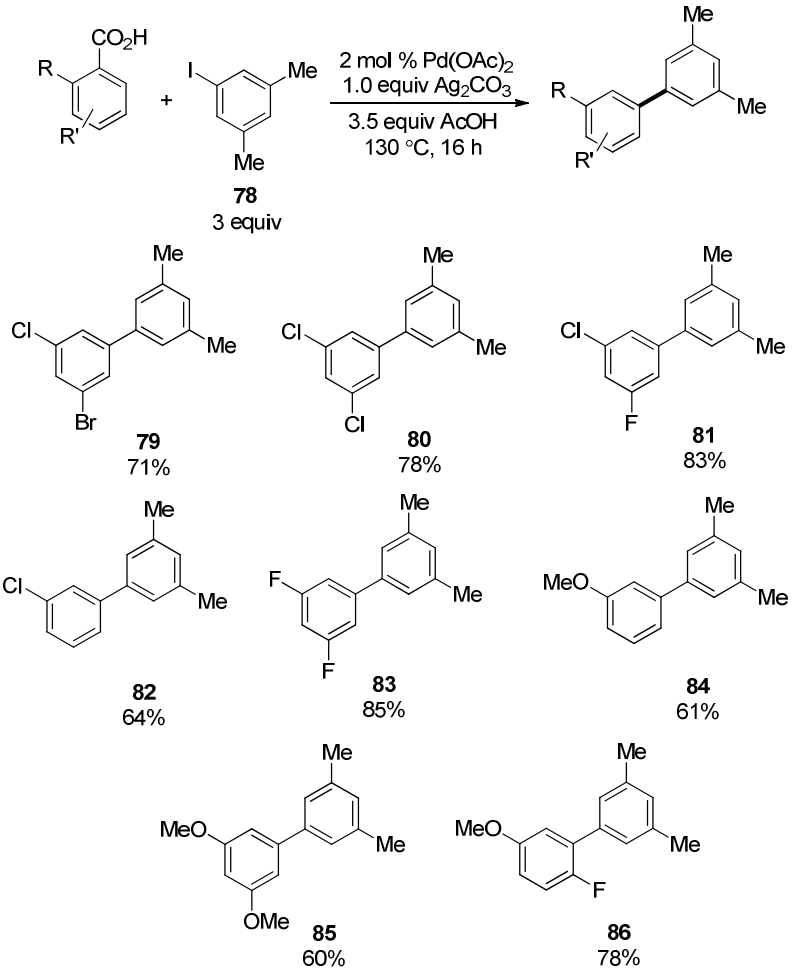


Scheme 109. Effect of the H_2O in the formal *meta*-selective C−H arylation. Yields determined by ^1H NMR using mesitylene as internal standard.

When 10 equiv of H_2O were added in the reaction, no benzoic acid starting material was recovered and the overall yield of the reaction was dramatically reduced to 20% affording protodecarboxylation of **74** as the main product (Scheme 109).

5.4. Scope of the formal *meta*-selective C−H arylation methodology

In order to test the scope of this methodology, different benzoic acids were subjected to the optimised conditions with iodoarene **78** as coupling partner. As demonstrated in previous chapters of this thesis, decarboxylative arylation methodologies are highly dependent on the substitution pattern in the benzoic acid (chapter 1). Since Ag(I) salts are able to decarboxylate benzoic acids bearing *ortho* electron-withdrawing and –donating groups, acids fulfilling this requirements were tested (Scheme 110).



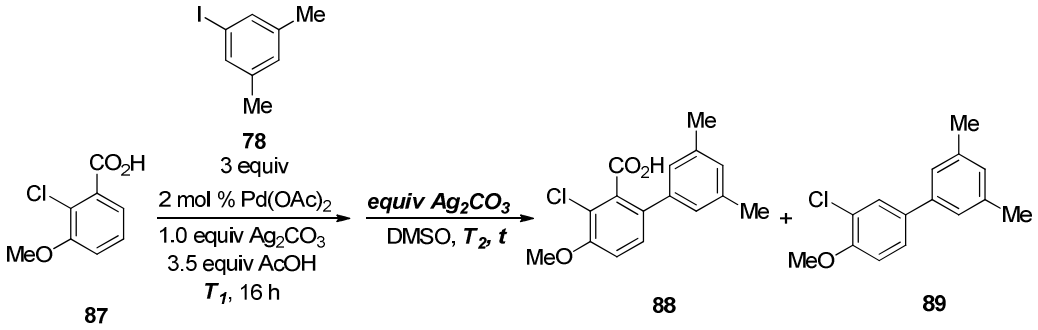
Scheme 110. Scope of the formal *meta*-selective C−H arylation with different benzoic acids. Yields of isolated pure material.

The, C–H arylation *meta* to a Cl substituent, which would offer an entry for further cross-couplings to be performed, occurs in high yields (**79**-**82**). Other acids such as 2,4-difluorobenzoic acid also led to the corresponding *meta*-arylated adduct **83**. This tandem transformation is not limited to electron-withdrawing groups in the *ortho* position of the starting benzoic acid: MeO is also compatible with our protocol, leading to *meta*-substituted biaryl compounds in good yields (**84**-**86**).

Benzoic acids bearing other *ortho*-substituents were also subjected to the reaction conditions. However, a slight modification of the reaction conditions had to be made in each particular case.

For example, 2-chloro-3-methoxybenzoic acid (**87**) needed further optimisation since

only 32% of **89** was observed when subjected to the standard conditions (Table 21, entry 1).

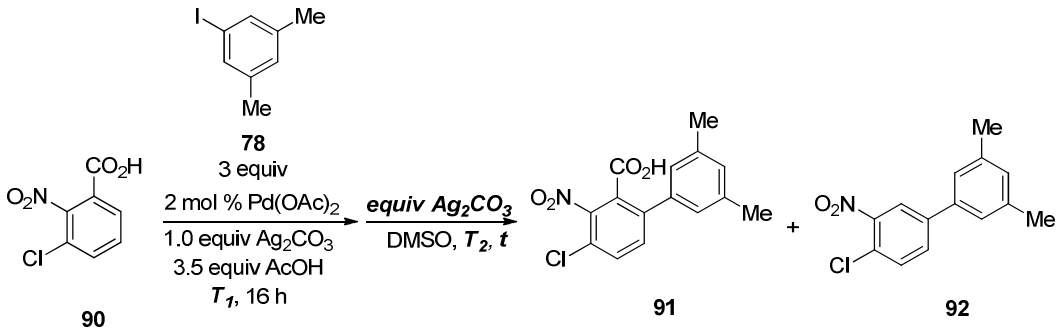


Entry	T_1	T_2	Time (t)	Ag_2CO_3	Yield of 88	Yield of 89
1	130 ºC	-	-	-	35%	32%
2	130 ºC	130 ºC	3 h	1.0	30%	38%
3	150 ºC	-	-	-	25%	43%
4	150 ºC	170 ºC	3 h	1.0	16%	60%

Table 21. Optimisation of the *meta*-selective arylation of benzoic acid **87**. Yields determined by ^{1}H NMR using mesitylene as internal standard.

Since we demonstrated that Ag(I) salts are capable of decarboxylating benzoic acids bearing an electron-withdrawing group at the *ortho* position (chapter 3), it was then hypothesised that the addition of extra Ag_2CO_3 would facilitate the decarboxylation of the remaining 35% arylated acid **88**. However, similar yields were obtained after the addition of Ag_2CO_3 in DMSO at the same temperature after 16 h (Table 21, entry 2). The reaction was carried out at 150 ºC and an increase of the yield of **89** was observed although 25% of **88** still remained (Table 21, entry 3). Subsequent addition of Ag_2CO_3 after 16 h at 170 ºC afforded the desired compound **89** in 60% yield. Unfortunately, further variations on the temperature did not lead to an improvement on the yield of **89**.

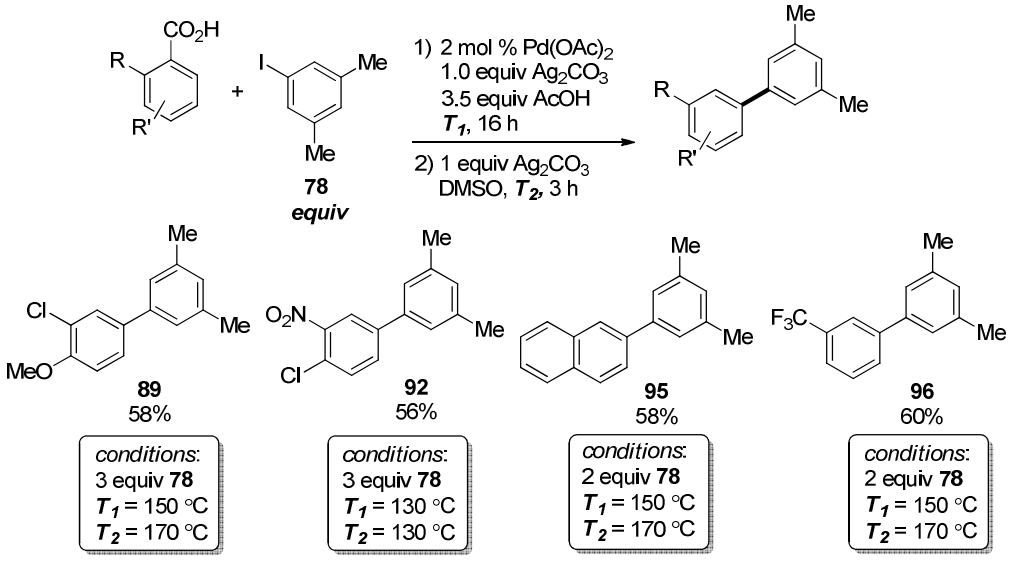
The reaction for 3-chloro-2-nitrobenzoic acid (**90**) was also optimised. In this case, however, the addition of Ag_2CO_3 after 16 h of reaction at 130 ºC afforded the desired product **92** in 60% yield (Table 22, entry 2).



Entry	T_1	T_2	Time (t)	Equiv Ag_2CO_3	Yield of 91	Yield of 92
1	130 ºC	-	-	-	44%	20%
2	130 ºC	130 ºC	3 h	1.0	0%	60%

Table 22. Optimisation of the *meta*-selective arylation of benzoic acid **90**. Yields determined by ^{1}H NMR using mesitylene as internal standard.

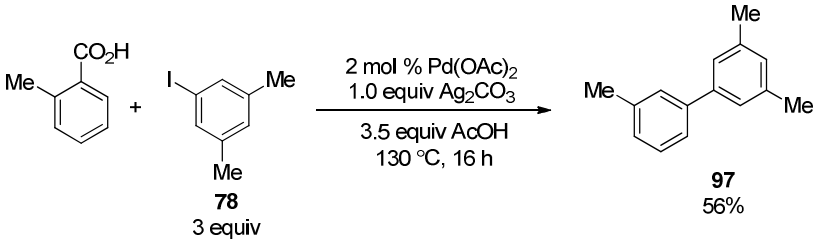
2-Naphthoic acid (**93**) and 2-trifluoromethylbenzoic acid (**94**) gave the best yields after carrying out the reaction at 150 ºC and subsequent addition of Ag_2CO_3 for 3 h in DMSO at 170 ºC. In these cases however, the amount of arylating agent was also optimised with 2 equiv of iodoarene being the optimal. Scheme 111 summarises the conditions for those acids that needed re-optimisation of the initial reaction conditions.



Scheme 111. Re-optimised conditions for the formal *meta*-selective arylation of benzoic acids. Yields of isolated pure material.

The scope of the reaction with respect to the iodoarene coupling partner was also examined. Iodoarenes substituted with F, Cl, Me, Br, and CO_2Me in *para* and *meta* positions are compatible with the procedure, and lead to the corresponding *meta*-substituted biaryl compounds in good yields. In all cases the *meta*-arylated adduct was the only regioisomer observed.[xi]

In order to map out the scope and limitation of the method, we tested a benzoic acid bearing an *ortho* alkyl group, which would not normally lead to protodecarboxylation in the presence of Ag(I) salts (chapter 3, Scheme 76). When *o*-toluic acid was subjected to the reaction conditions, compound **97** was obtained in 56% yield (Scheme 112). This result led us to reconsider our hypothesis of the Ag(I) being responsible for the decarboxylation, since our Ag(I)-catalysed protocol did not afford the decarboxylated product from *o*-toluic acid (compound **46**, Scheme 76).



Scheme 112. Formal *meta*-arylation of o-toluic acid.

5.5. Studies towards the mechanism of the formal *meta*-selective C−H arylation methodology

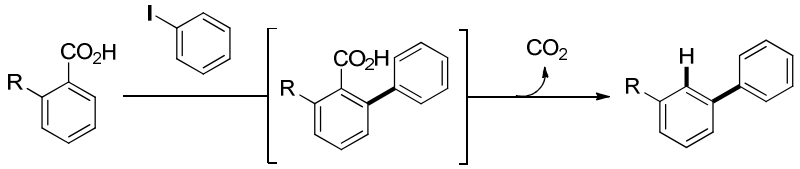
As mentioned in previous chapters, Ag salts are able to decarboxylate benzoic acids bearing *ortho* electron-withdrawing and -donating groups. However, the striking result obtained for *o*-toluic acid, where it is shown that **97** is obtained in 56% yield, led us to question the sequence of steps leading to the *meta*-arylated product, as well as the role of the transition-metal salts within the system. Therefore, a thorough analysis was needed in order to address these observations. This analysis would also lead to a better understanding of the unusual chemoselectivity observed in the

[xi] The scope of this methodology in relation to the iodoarene coupling partner was studied by Marika Righi (PhD student, Universittá di Urbino).

decarboxylation of the arylated acid over the starting benzoic acid.

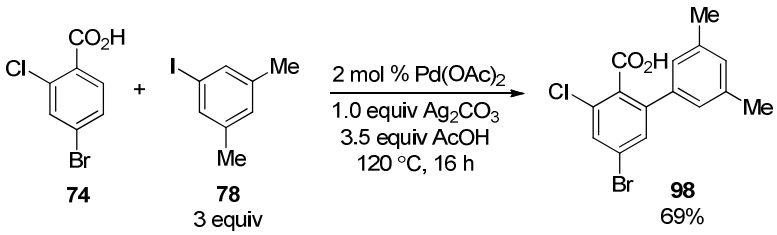
5.5.1. Decarboxylation step

The identification of arylated benzoic acid led us to hypothesise that this process is likely to proceed by a tandem *ortho*-arylation/protodecarboxylation, as depicted in Scheme 113.

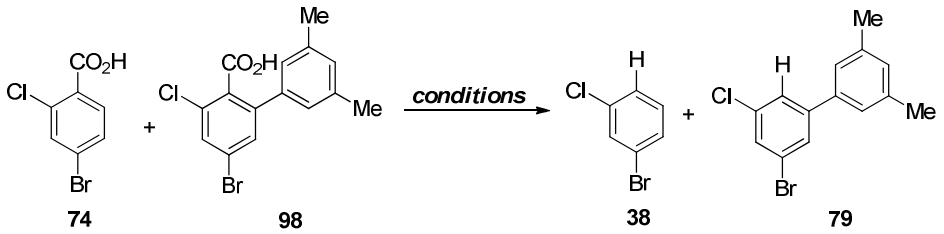


Scheme 113. Reaction pathway for the *meta*-selective C−H arylation.

To explain the high chemoselectivity displayed for the protodecarboxylation step between the starting benzoic acid and the arylated acid, we hypothesised that the decarboxylation of the more hindered substrate was much faster than the starting material. To address this issue, arylated acid **98** was synthesised using the *meta*-selective protocol conditions but at lower temperatures (Scheme 114). Subsequently, competition experiments between benzoic acid **74** and arylated acid **98** were carried out (Table 23).



Scheme 114. Synthesis of **98** via *ortho*-arylation of **74** with **78**.



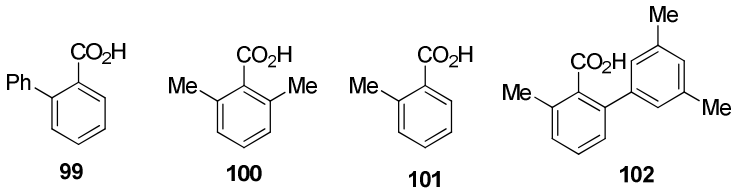
Entry	$Pd(OAc)_2$	Ag_2CO_3	Solvent	T (°C)	Time	Yield of 38	Yield of 79
1	-	10 mol %	DMSO	120	4 h	18%	5%
2	-	1.0 equiv	AcOH	130	2 h	0%	0%
3	2 mol %	-	AcOH	130	2 h	0%	22%
4	2 mol %	1.0 equiv	AcOH	130	16 h	0%	5%

Table 23. Competition experiments between **74** and **98**.

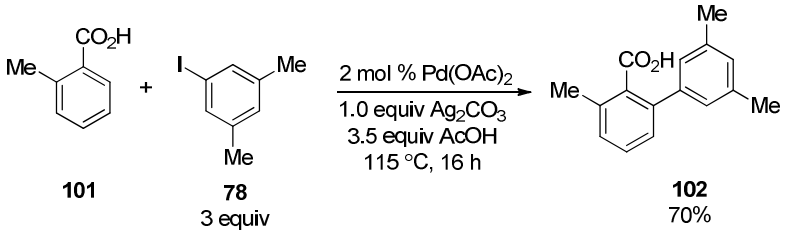
At the onset, a mixture of **74** and **98** was subjected to our previously reported Ag-mediated protodecarboxylation conditions (10 mol% Ag_2CO_3 in DMSO). As expected, **38** was obtained preferentially over **79** in a 3:1 ratio (Table 23, entry 1). However, when AcOH was used as the solvent, no protodecarboxylation of **74** or **98** was observed (Table 23, entry 2). This result confirmed our supposition about the Ag not being responsible for the decarboxylation step in this process. Moreover, when **74** and **98** were treated with 2 mol % of $Pd(OAc)_2$ in AcOH, protodecarboxylation of **98** was observed with complete selectivity (Table 23, entry 3). This selectivity suggests that electronics are not the only factor controlling the Pd-mediated decarboxylation of benzoic acids but also sterics factors contribute to this particular step. When both benzoic acids were subjected to the reaction conditions, the same selectivity was observed (Table 23, entry 4). However, the marked decrease in the decarboxylation rate could be caused by a fast formation of a palladacycle with the Ag salt of **74** (*vide infra*), sequestering the Pd catalyst.

In light of these observations it was then hypothesised that Pd may be the metal responsible for the decarboxylation step of the arylated acid. As mentioned before, electronics as well as sterics could play an important role in the reaction. Therefore, to further verify this hypothesis, different benzoic acids were subjected to decarboxylation in the presence of catalytic amounts of $Pd(OAc)_2$ in AcOH. 2-

Phenylbenzoic acid (**99**), 2,6-dimethylbenzoic acid (**100**), *o*-toluic acid (**101**) and benzoic acid **102** were chosen for this reaction (Scheme 115). Benzoic acid **102** was readily obtained via arylation of **101** (Scheme 116).

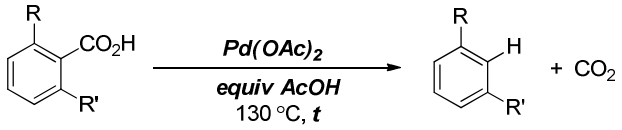


Scheme 115. *Ortho*-substituted benzoic acids tested on the Pd-catalysed protodecarboxylation.



Scheme 116. Formation of **102** via *ortho*-arylation of *o*-toluic acid (**101**).

The results of the decarboxylation tests are outlined in Table 24.



Entry	Acid	R/R'	$Pd(OAc)_2$	AcOH	t	Yield of product
1	**100**	Me/Me	2 mol %	14 equiv	2 h	12%
2	**100**	Me/Me	2 mol %	14 equiv	16 h	54%
3	**100**	Me/Me	2 mol %	7 equiv	16 h	64%
4	**100**	Me/Me	-	14 equiv	16 h	0%
5	**99**	Ph/H	2 mol %	14 equiv	16 h	0%
6	**101**	Me/H	2 mol %	14 equiv	16 h	0%
7	**102**	Me/3,5-xylyl	2 mol %	14 equiv	16 h	42%

Table 24. Pd-catalysed protodecarboxylation experiments for acids **99-102**.

Surprisingly, when benzoic acid **100**, was mixed with 2 mol % $Pd(OAc)_2$ in 14 equiv

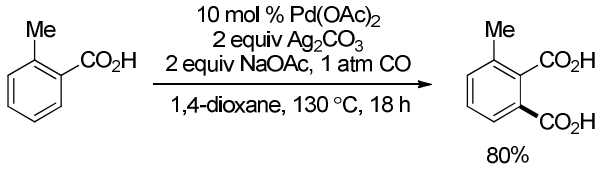
of AcOH, 12% of decarboxylated product was detected after 2 h of reaction (Table 24, entry 1). A 54% of protodecarboxylated product was obtained when the reaction was subjected to longer reaction times (Table 24, entry 2). A decrease of the amount of AcOH led to a slight rise in the yield (Table 24, entry 3). It is noteworthy that a control experiment showed no decarboxylation in the absence of Pd catalyst (Table 24, entry 4). Mono-substituted acids bearing a Me or a Ph (**99** and **101**) failed to react under these reaction conditions (Table 24, entries 5 and 6). In agreement with the previous observations (Table 23), when hindered benzoic acid **102** was subjected to the reaction conditions, 42% of the protodecarboxylated biaryl was obtained, with the rest of the material being unreacted starting material.

The fact that benzoic acid **100** decarboxylates in the presence of $Pd(OAc)_2$/AcOH, led us to hypothesise that sterics and possibly not electronics are the key factors in this decarboxylation step. However, due to time constraints, further studies on the mechanism were not possible, and this is currently under investigation by other members of the reseach group.

5.5.2. *ortho*-Directed C−H arylation step

The first step in this tandem process is an *ortho*-directed arylation, mediated by the carboxylic acid group.

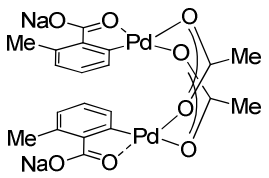
Recently, Yu and co-workers developed a methodology for the *ortho*-carboxylation of benzoic acids (Scheme 117).[63b]



Scheme 117. *ortho*-Carboxylation of benzoic acids.

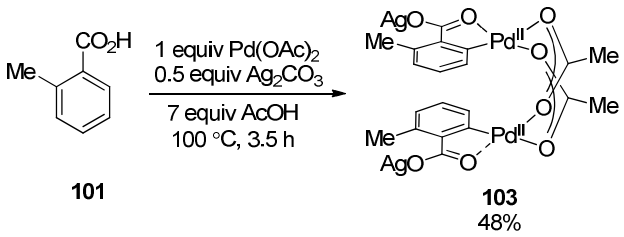
The authors claimed that this process proceeds via the formation of the dimeric

palladacycle depicted in Scheme 118.



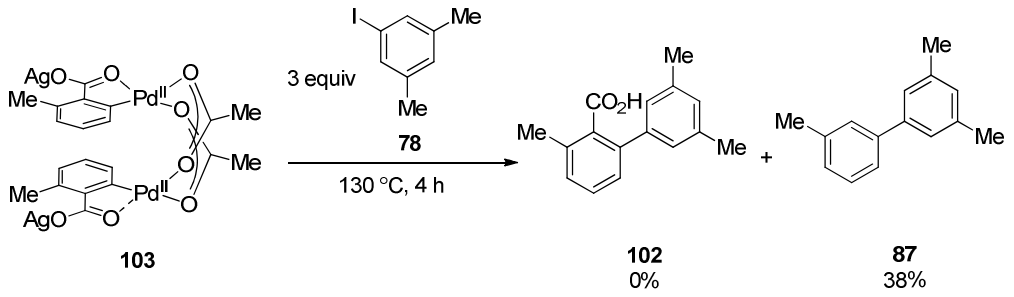
Scheme 118. Dimeric palladacycle of *o*-toluic benzoic acid proposed by Yu and co-workers.

The formation of a similar palladacycle was envisaged in our system, where the Na cation was replaced with Ag. The synthesis and isolation of such palladacycle was attempted. It was found that upon mixing *o*-toluic acid **101** with 1 equiv of $Pd(OAc)_2$ and 0.5 equiv Ag_2CO_3 in AcOH at 100 ºC afforded 48% of a highly insoluble solid, which was attributed to compound **103** (Scheme 119). The high insolubility of this compound in a large amount of solvents (CH_2Cl_2, $CHCl_3$, Et_2O, MeOH, EtOAc, CH_3CN, dioxane, DMF, acetone, etc.) presented great difficulties in characterisation. However, ^1H, ^{13}C NMR and IR were obtained in DMSO-d_6. The data obtained were then compared with palladacycle in Scheme 118 and supported the formation of **103** (Scheme 119).



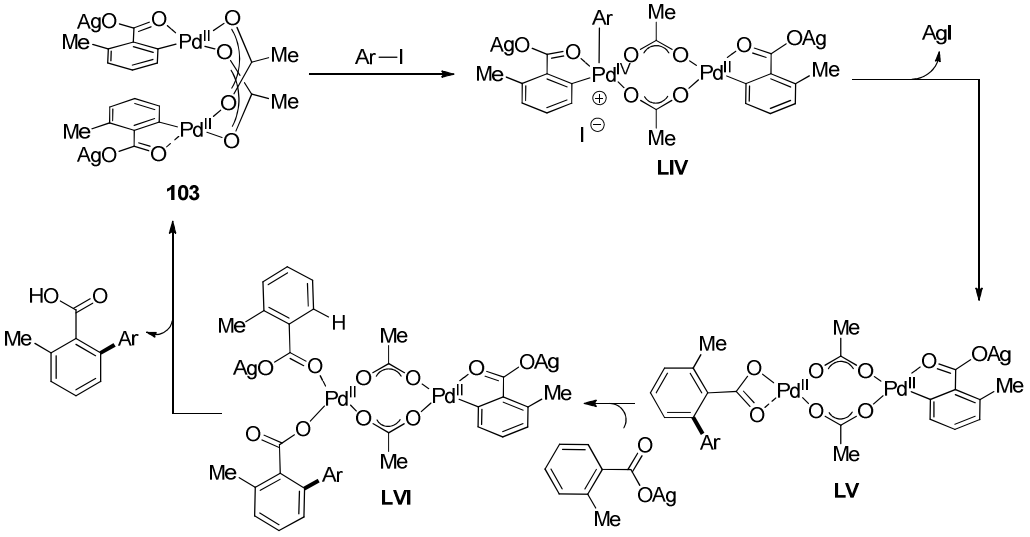
Scheme 119. Formation of palladacycle **103**.

This solid was then subjected to arylation with iodoarene **78**. Since **78** is a liquid, no AcOH was added to prevent the protodemetalation of palladacycle **103**. After 4 h, 38% of product **87** was obtained, with no trace of arylated acid **102** (Scheme 120). This result led us to believe that an initial formation of a palladacycle is indeed occurring in the *meta*-selective C−H arylation protocol.



Scheme 120. Arylation of **103** with **78**.

At this stage, two possible mechanisms for the arylation process were considered. The first possible pathway would involve a Pd(II)/Pd(IV) catalytic system. Based on previous reports by Sanford and co-workers on C−H arylation of 2-phenylpyridines with iodonium(III) species,[85] we hypothesised the mechanism depicted in Scheme 121.

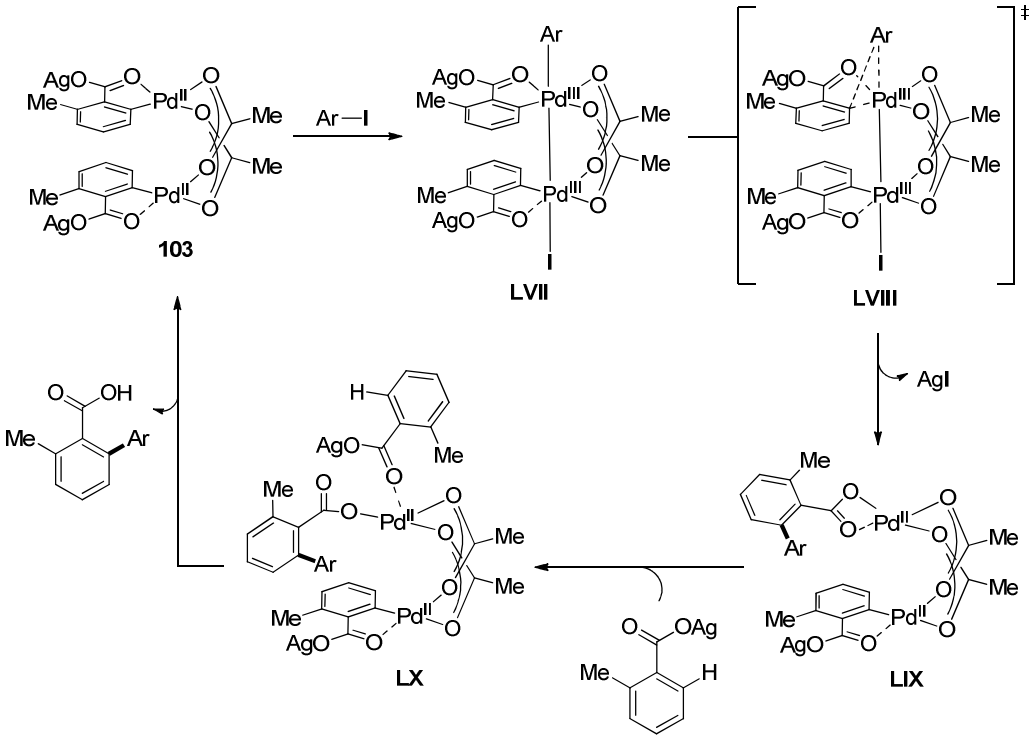


Scheme 121. Pd(II)/Pd(IV) mechanistic proposal.

It has been demonstrated that aryl iodides can undergo oxidative addition into Pd(II) to generate aryl-Pd(IV) complexes.[86] Therefore, oxidative addition into **103** would generate cationic species **LIV**, which consist of a Pd(IV) centre attached to the other bridging Pd(II) centre (Scheme 121). At this stage, reductive elimination from the Pd(IV) centre affords the arylated product with concomitant formation of AgI (**LV**).

Then, **LV**, coordinates to another Ag-carboxylate molecule generating intermediate **LVI**. Subsequent *ortho* C−H activation regenerates the bimetallic complex **103**.

Recently, Ritter and co-workers have reported that Pd-catalysed carbon−halogen bond forming reactions could proceed via a Pd(II)/Pd(III) system.[87] In light of these observations, another possible pathway was proposed (Scheme 122). In a first stage, oxidative addition by the aryl iodide on **103** would generate a Pd(III)−Pd(III) bimetallic complex **LVII**. **LVII** would undergo reductive elimination to give **LIX** via transition state **LVIII** with concomitant formation of AgI. Another molecule of Ag-carboxylate coordinates with a Pd centre to afford complex **LX**, which after C−H activation regenerates **103**.



Scheme 122. Pd(II)/Pd(III) mechanistic proposal.

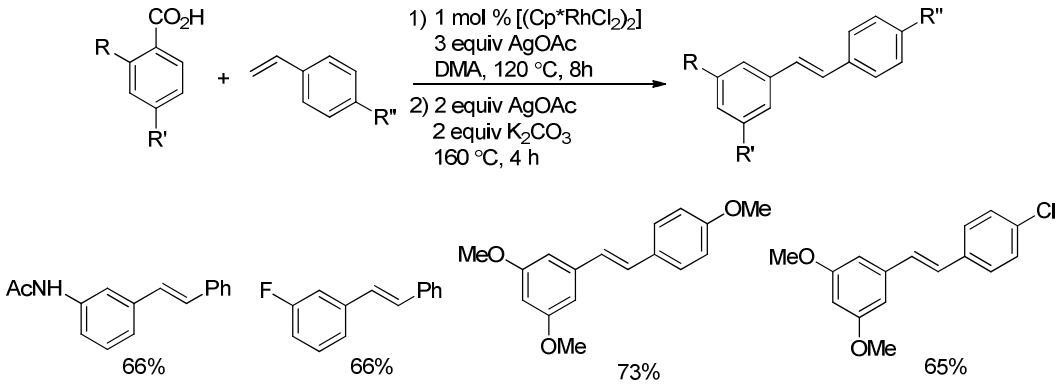
Despite the studies by Ritter and co-workers on the role of Pd(III)−Pd(III) complexes in Pd-catalysed reactions, they are still limited to the formation of carbon−heteroatom bonds. There is currently no precedent to support the hypothesis of a Pd(II)/Pd(III) system for the formation of C−C bonds. In addition, no examples have been reported on the oxidative addition of aryl iodides into Pd(II) centers to form bimetallic Pd(III)

species.

In summary, it was demonstrated that the *meta*-selective C−H arylation protocol for *o*-toluic acid (**101**) could proceed via a tandem arylation/decarboxylation process. The first step, an *ortho*-directed C−H arylation, is believed to proceed via the formation of a palladacycle such as **103**. Arylation of **103** affords the desired biaryl **87**. It was also demonstrated that the decarboxylation step is mediated by the Pd catalyst and it may be controlled by steric factors, although further studies are needed to understand the specific reactivity of hindered benzoic acids.

5.6. Concurrent work by other research groups

During the presented work on the *meta*-selective arylation methodology, a similar approach was developed by Miura, Satoh and co-workers. The authors reported a tandem process for the formal *meta* olefination of arenes via *ortho* vinylation of benzoic acids followed by decarboxylation (Scheme 123).[88]



Scheme 123. Formal *meta*-alkenylation of arenes via a one-pot vinylation/decarboxylation.

As found in our method, *ortho*-substituted benzoic acids were successfully coupled with different styrene derivatives to afford the *meta*-vinylated products in high yields.

This two-step reaction proceeds via a Rh-catalysed *ortho* C−H vinylation of the benzoic acid followed by a Ag-mediated decarboxylation step.

5.7. Conclusions

This chapter presents the development of the first method for the formal *meta*-selective direct C–H arylation of arenes using aryl iodides as coupling partners. This process, which is compatible with a wide range of *meta* substituents, utilises carboxylic acids as traceless directing groups to afford complete control upon the regioselectivity of the direct C–H arylation. The low cost and ready availability of benzoic acids as starting materials provides an efficient alternative to the sometimes (prohibitively) expensive Suzuki couplings, to access *meta*-substituted biaryl compounds. The synthesis of the boronic acids or esters prior to the Suzuki cross-coupling generally involves several steps, which is reflected in their higher cost. For example, in the case of compound **84**, 3-methoxyphenylboronic acid costs £2,310 per mole whereas 2-methoxybenzoic acid costs £24 per mole.

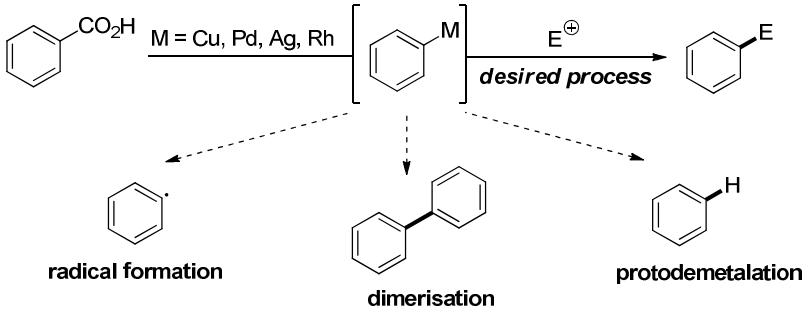
Furthermore, it has been demonstrated that Pd salts (and not Ag) are able to perform the decarboxylation of *ortho*-arylated disubstituted/hindered benzoic acids under the reported reaction conditions. Also, this decarboxylation occurs with complete chemoselectivity over the starting *ortho*-monosubstituted benzoic acids.

This work presents a significant advance in the area of C−H arylation methodologies since the regioselectivity is completely controlled. In future work, this approach could be applied to all the methodologies involving *ortho*-functionalisation of benzoic acids thereby, affording *meta*-substituted arenes with high degree of selectivity.

Chapter 6. Au(I)-mediated C−CO_2H bond activation: decarboxylative auration of (hetero)aromatic carboxylic acids

6.1. Introduction

It has been shown in previous chapters that the use of benzoic acids as aryl synthons has arisen as a powerful tool for organic synthesis. Nevertheless, the great majority of these transformations still suffer from several drawbacks. One of the most important limitations is the need for very high temperatures (180–190 °C). Pd-, Cu- or Rh-catalysed decarboxylative methods also suffer from very low substrate compatibility. In the case of Pd-catalysed decarboxylative couplings, dimerisation of the carboxylic acid is a highly competitive side-reaction. When Ag is mediating the decarboxylation step, the instability of the aryl-Ag and the tendency for protodemetalation present an enormous drawback. Overall, these undesirable processes significantly lower the yields of the subsequent transformations (Scheme 124).

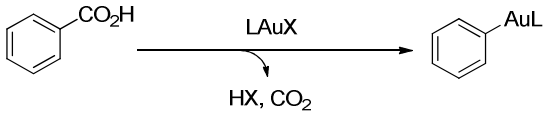


Scheme 124. Decarboxylative transformations versus undesired side reactions.

Therefore, a general method for the activation of C−CO_2H bonds leading to more stable aryl-metal intermediates is highly desirable.

6.2. Aims of the project

It has been shown that Cu(I) and Ag(I) salts are able to decarboxylate (hetero)aromatic carboxylic acids, to form the corresponding aryl-metal species (chapter 1).[17] A close inspection of these metals reveals that both have d^{10} electronic configuration. Therefore, it was envisaged that their isolectronic group 11 partner, Au(I), may also be able to mediate decarboxylative activation of C−CO_2H bonds (Scheme 125).



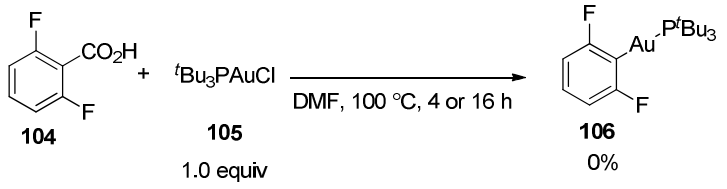
Scheme 125. Au(I)-mediated decarboxylation of benzoic acids.

Previous experience in our research group with aryl-Au(I) complexes, led us to believe that the resulting aryl-Au(I) species would be significantly more stable than their Ag, Cu or Pd counterparts,[89] thus reducing the side reactions observed when further transformations are attempted.

It is worth mentioning that previous reports on Au(I) decarboxylations dating from 1991, indicated that Ph_3PAu-OCOPh invariably resulted in deposition to Au(0) and radical-mediated processes when heated under reflux in toluene.[90] However, despite this potential pitfall, we set out to explore the possibility of using Au(I) salts to catalyse the activation of C-CO_2H bonds.

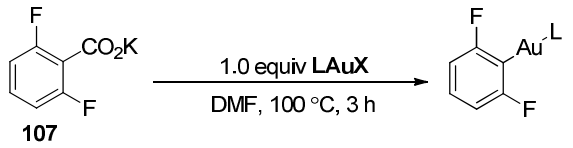
6.3. Optimisation of the Au(I)-mediated decarboxylative auration of arenes

Initially, the reaction between 2,6-difluorobenzoic acid (**104**) with Au complex **105** was explored. However, no auration product **106** was observed after 4 or 16 h at 100 ºC (Scheme 126), after which time only unreacted starting material **104** was recovered.



Scheme 126. Decarboxylative auration of **104** with Au(I) complex **105**.

It was envisaged that the potassium salt of the parent carboxylic acid would facilitate ligand exchange with the Au(I) complex, in order to form the Au(I) carboxylate. Various Au(I) salts were tested and the results are summarised in Table 25.

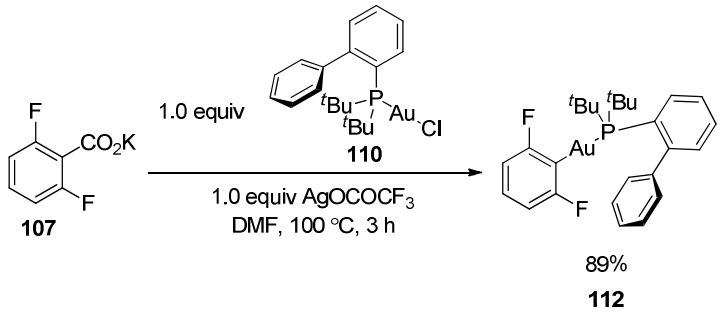


Entry	LAuX	Yield of the aryl-Au(I) complex[a]
1	$^{t}Bu_3PAuCl$ (**105**)	0%
2	IPrAuCl (**108**)	0%
3	Ph_3PAuCl (**109**)	0%
4	*o*-Ph-C_6H_4($^{t}Bu)_2PAuCl$ (**110**)	0%
5	{[*o*-Ph-C_6H_4($^{t}Bu)_2P$](CH$_3$CN)Au}SbF_6 (**111**)	98% (92% isolated)

Table 25. Optimisation of the Au(I)-mediated decarboxylative auration. [a] Yields determined by ^{1}H NMR using mesitylene as internal standard.

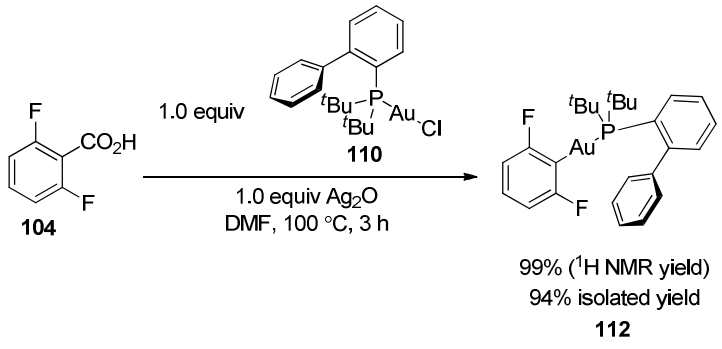
Au(I) chloride salts **105**, **108**, **109** and **110** were found to be inactive when heated at 100 °C in DMF (Table 25, entries 1 to 4). When the commercially available cationic Au(I) species *o*-Ph-C_6H_4-^{t}BuPAuSbF$_6$:MeCN, **110**, was subjected to the same reaction conditions, the corresponding aryl-Au(I) was obtained in 92% isolated yield (Table 25, entry 5). This result led us to believe that the use of a cationic Au(I) species was necessary for the decarboxylation to proceed.

It was then hypothesised that the addition of a Ag salt would generate the desired cationic Au(I) species from the parent Au(I) chloride salt, with concomitant formation of AgI. Indeed, when 1 equiv of $AgOCOCF_3$ was added to the reaction mixture with complex **110**, 89% of the desired complex was obtained (Scheme 127).



Scheme 127. Effect of the Ag salt on the Au(I)-mediated decarboxylative auration. Yield determined by ^{1}H NMR using mesitylene as internal standard.

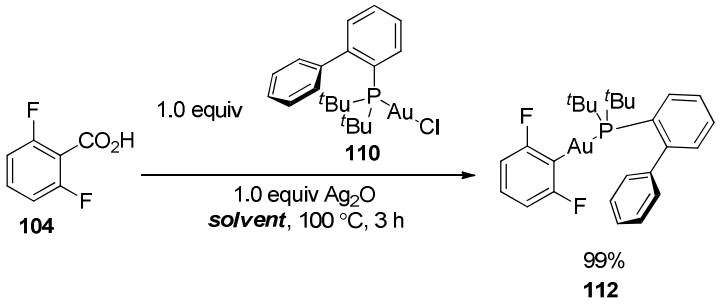
However, the potassium salt of the benzoic acid was still necessary thus requiring an extra synthetic step. Therefore, it was envisaged that the more basic Ag_2O (relative to $AgOCOCF_3$) would allow the use of the carboxylic acid as the starting material. Therefore, the reaction with 1.0 equiv of Ag_2O was attempted using acid **104**.



Scheme 128. Effect of the Ag_2O on the decarboxylative auration of **104**.

As depicted in Scheme 128, by using 1.0 equiv of Ag_2O the reaction afforded the aryl Au(I) **112** in 94% isolated yield (the effect of Ag in this system is discussed in detail in section 6.5). Unfortunately, when lower amounts of Ag_2O were tested, very low yields of the decarboxylative auration product were obtained.

Subsequently, a screening of different solvents was performed. The results are summarised in Table 26.



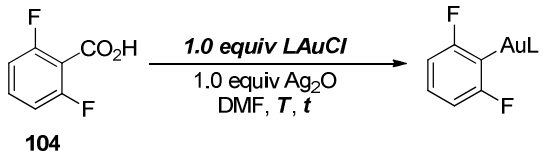
Entry	Solvent	Yield of 112[a]
1	DMF	99%
2	DMSO	95%
3	NMP	96%
4	Toluene	0
5	1,4-dioxane	<5%

Table 26. Optimisation of the solvent for the decarboxylative auration of **104**. [a] Yields were determined by ^{1}H NMR using mesitylene as internal standard.

A survey of solvents identified that polar or coordinating solvents afforded excellent yields of **112** (Table 26, entries 1, 2 and 3). However, when apolar solvents were used instead, the reactivity was dramatically reduced, resulting in the recovery of starting material unreacted (Table 26, entries 3 and 4).

Having demonstrated that Au(I) is able to mediate the activation of C−CO_2H bonds (Table 25, entry 5), it was envisaged that the ligand on the Au could have an influence on the temperature of the decarboxylation step. Therefore, we set out to explore this process at different temperatures using different ligands. It is worth

mentioning that due to the great number of commercially available Au(I) chloride salts, the protocol using 1.0 equiv of Ag_2O was chosen for this process. The results are shown in Table 27.



104

Entry	LAuCl	Temp. (T)	Time (t)	Yield of aryl-Au(I)[a]
1	*o*-Ph-C_6H_4(^{t}Bu)$_2$PAuCl (**110**)	100 ºC	3 h	94%[b]
2	*o*-Ph-C_6H_4(^{t}Bu)$_2$PAuCl (**110**)	70 ºC	20 h	93%
3	*o*-Ph-C_6H_4(^{t}Bu)$_2$PAuCl (**110**)	60 ºC	40 h	36%
4	Et_3PAuCl (**113**)	100 ºC	3 h	97%[b]
5	Et_3PAuCl (**113**)	60 ºC	20 h	29%
6	Ph_3PAuCl (**109**)	100 ºC	2 h	95%[b]
7	Ph_3PAuCl (**109**)	60 ºC	20 h	37%
8	IPrAuCl (**108**)	100 ºC	2 h	98%[b]
9	IPrAuCl (**108**)	60 ºC	20 h	37%
10	^{t}Bu$_3$PAuCl (**105**)	100 ºC	2 h	94%[b]
11	^{t}Bu$_3$PAuCl (**105**)	70 ºC	16 h	95%
12	^{t}Bu$_3$PAuCl (**105**)	60 ºC	20 h	53%
13	^{t}Bu$_3$PAuCl (**105**)	60 ºC	40 h	99%
14	^{t}Bu$_3$PAuCl (**105**)	50 ºC	60 h	53%

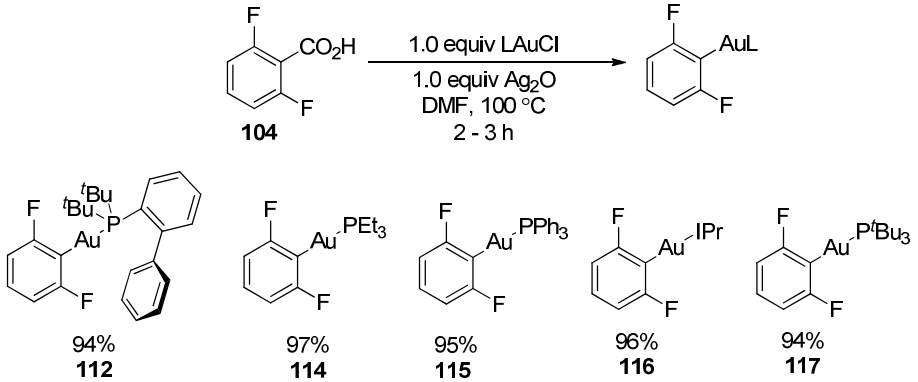
Table 27. Ligand influence on the reaction temperature in the Au(I)-mediated decarboxylative auration. [a] Yields determined by ^{1}H NMR using mesitylene as an internal standard. [b] Yields of isolated pure material.

As depicted in Table 27, when the decarboxylation was attempted using Au(I) chloride **110** at 70 ºC, aryl-Au(I) complex was obtained quantitatively, albeit longer reactions times were required (Table 27, entries 1 and 2). We were pleased to observe that when the temperature was lowered to 60 ºC, a 36% yield of the desired aryl-Au(I) complex was still obtained after 40 h of reaction (Table 27, entry 3). A similar trend was observed in complexes **113**, **109**, **108** and **105**; when the reaction was carried out

at 100 ºC, near quantitative yields of the desired aryl-Au(I) were observed (Table 27, entries 4, 6, 8 and 10). However, moderate yields were obtained when the reaction was carried out at 60 ºC (Table 27, entries 5, 7, 9). $^{t}Bu_3PAuCl$ (**105**) proved to be more reactive than the other Au(I) chloride salts (Table 27, entry 11 and 12), affording quantitative yields of the aryl-Au(I) complex at 60 ºC when the reaction time was increased to 40 h (Table 27, entry 13). It is noteworthy that **105** was able to mediate the decarboxylation step even at 50 ºC. In this case, 60 h reaction time was needed to afford 53% of the product (Table 27, entry 14).

This remarkable decrease on the decarboxylation temperature (when compared to Cu, Pd or Ag protocols) by simply changing the ligand at the Au centre opens the door to the design of new ligands that could potentially lead to much milder decarboxylative transformations (see chapter 7).

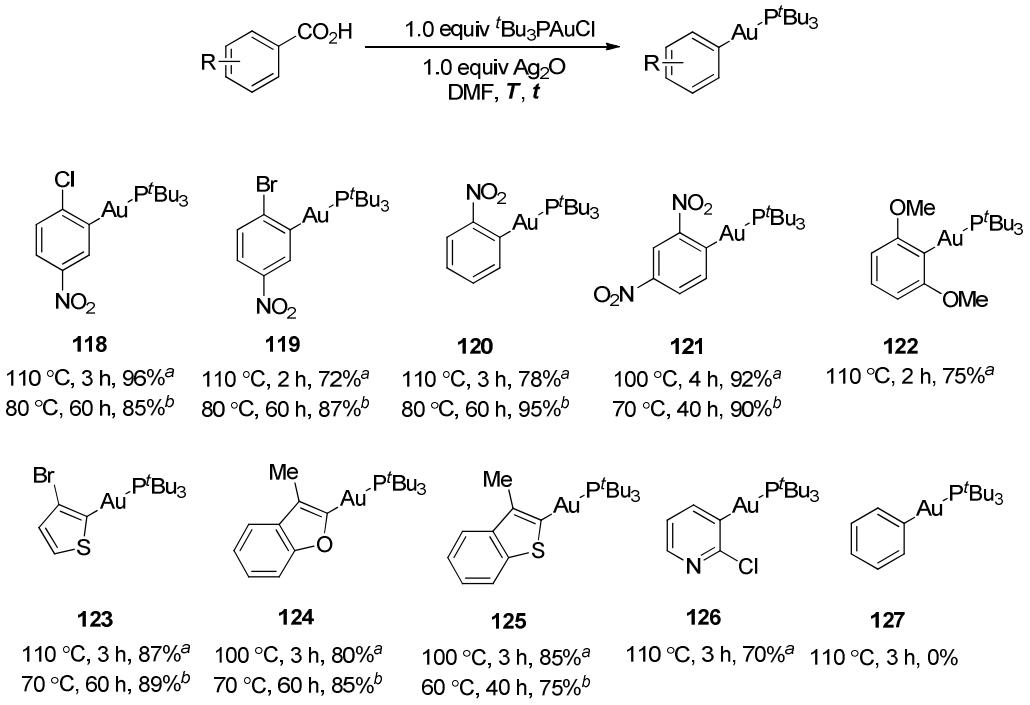
In summary, Au(I) chloride salts bearing ligands of different types were demonstrated to mediate the decarboxylation step for benzoic acid **104**, affording excellent yields of the desired auration product. It is noteworthy that complexes **112**, **114-117** were easily purified by silica gel column chromatography, highlighting the great stability of these compounds towards protodemetalation. Scheme 129 summarises the results obtained when the reaction was carried out at 100 ºC.



Scheme 129. Ligand scope of the Au(I)-mediated decarboxylative auration.

6.4. Scope of the Au(I)-mediated decarboxylation

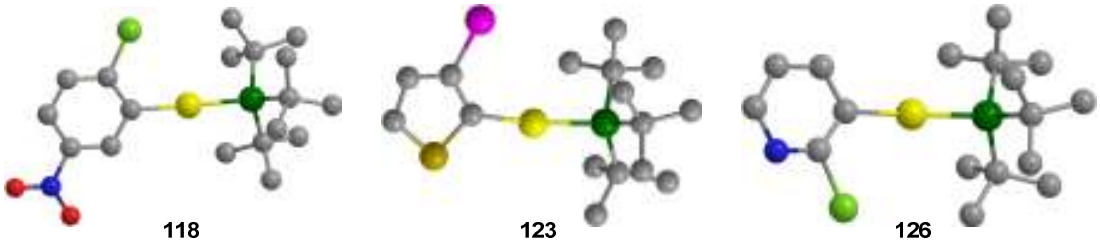
Having optimised the protocol for the Au(I)-mediated decarboxylation of **104**, the scope of this reaction was explored with various carboxylic acids. The reactions were performed both at 110 °C (which required shorter reaction times compared to 100 °C) and at lower temperatures to test the lower limits for decarboxylation. The results are outlined in Scheme 130.



Scheme 130. Scope of the Au(I)-mediated decarboxylative auration. [a] Yields of isolated pure material. [b] Yields determined by ^{1}H NMR using mesitylene as an internal standard.

The reaction protocol was compatible with benzoic acids bearing *ortho* electron-withdrawing and –donating substituents, such as Cl, Br, NO_2 and MeO (**118**, **119**, **120**, **121** and **122**), affording the corresponding aryl-Au(I) in excellent yields. Benzoic acid, on the other hand, with no *ortho* substituents, failed to react (**127**). Heteroaromatic carboxylic acids were also found to undergo decarboxylative auration under the reaction conditions (**123**, **124**, **125** and **126**), on the condition that the carboxylic acid is α to a heteroatom or *ortho* to an electron-withdrawing group. It is remarkable that the reaction temperatures could be lowered to 60−80 °C without affecting the yield of the product. In the case of **122** and **126**, no reaction was observed at temperatures lower than 110 °C.

Crystal structures were obtained for compounds **118**, **123** and **126** thereby confirming the connectivity of the Au(I) atom in the arene (Scheme 131).



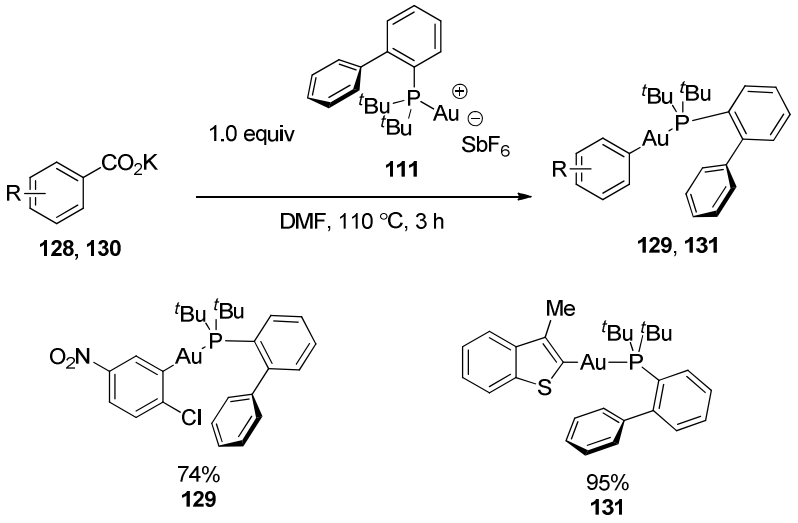
Scheme 131. X-Ray structures of compounds **118**, **123** and **126**.

The requirement of an *ortho* electron-withdrawing or –donating group, or an α heteroatom for the decarboxylation to proceed, suggests a similar pattern of chemoselectivity to that observed previously for Ag-mediated decarboxylations, but without the disadvantage of protodemetalation.

6.5. Mechanistic investigations

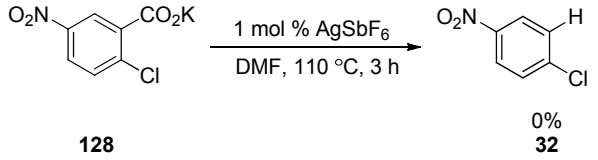
Our initial experiments using the cationic Au(I) salt **111** (Table 25, entry 5) showed that Au(I) alone is able to mediate the decarboxylative activation of potassium salt **107.** To confirm the generality of this Ag-free decarboxylative process, the potassium salts of 2-chloro-5-nitrobenzoic acid, **128**, and 3-methylbenzothiophene-2-carboxylic

acid, **130**, were subjected to the reaction conditions depicted in Table 25, entry 5 (Scheme 132).



Scheme 132. Au(I)-mediated decarboxylation of **128**, **130**. Yields of isolated pure material.

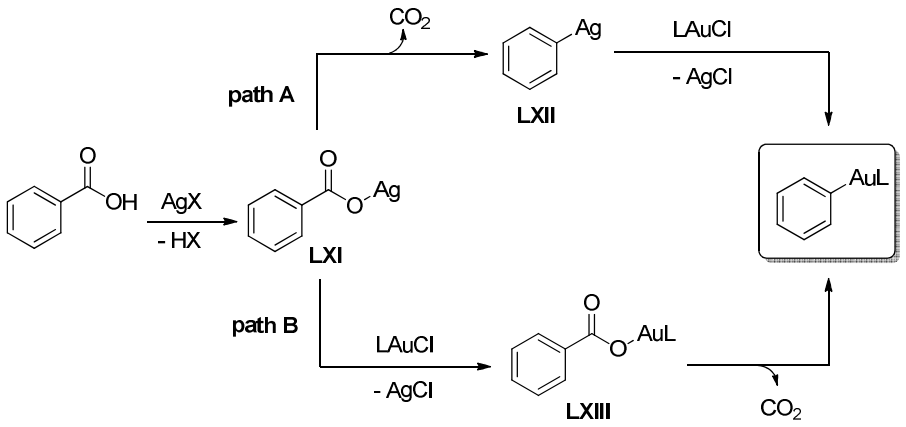
The reaction afforded excellent yields of **129** and **131** (74% and 95% respectively). However, in light of recent examples, where reactivity initially attributed to Au or Fe has been shown to originate from trace impurities of Pd or Cu,[91] respectively, and given the similarity in the chemoselectivity pattern observed when compared with Ag(I)-mediated decarboxylations (chapter 3), we decided to investigate the possibility of traces of Ag(I) impurities being responsible for this decarboxylation process. Au complex **111** and the carboxylate salt **128** were analysed by atomic absorbance spectroscopy, which showed a content of Ag of <0.01%. In light of this observation, a protodecarboxylation control experiment was then carried out by adding 1 mol % of $AgSbF_6$ to the system resulting in the complete recovery of the starting material **128** (Scheme 133).



Scheme 133. Control experiment using $AgSbF_6$.

This experiment confirms that Au(I), and not Ag(I), is responsible for the activation of the C−CO_2H bond.

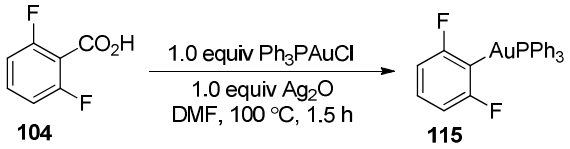
Although these experiments prove that cationic Au(I) is able to mediate the decarboxylation step, it is not clear that this is the case when using the protocol which employs Ag_2O as an additive (Table 25, 26 and 27). In these cases, two possible reaction pathways can be envisaged (Scheme 134).



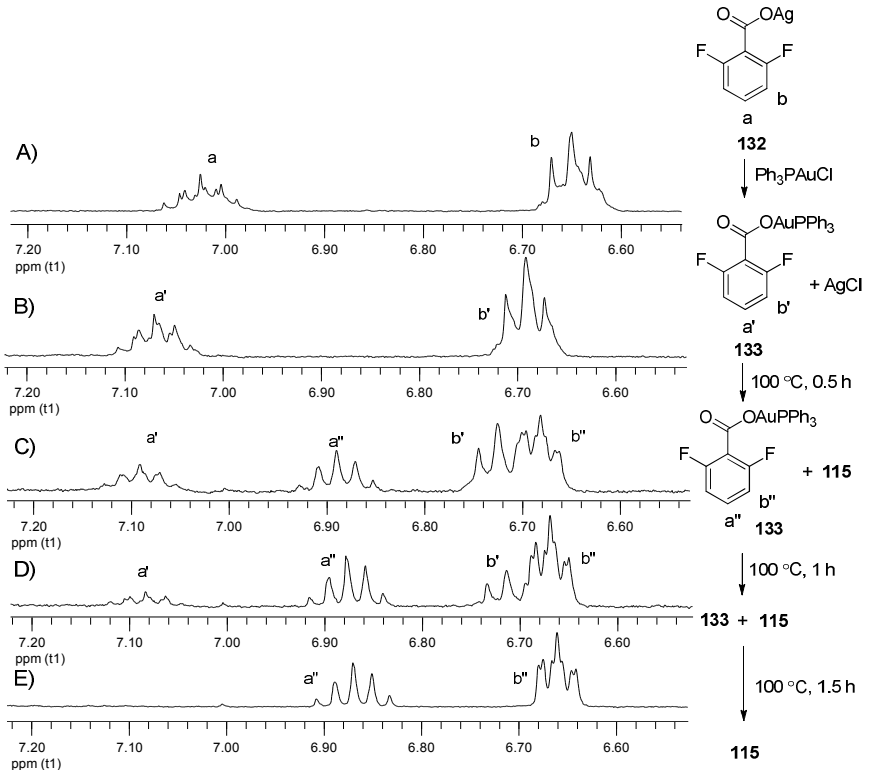
Scheme 134. Two proposed pathways for the decarboxylative auration in the presence of Ag(I) salts.

Initially, the Ag(I) salt **LXI**, will be formed, by reaction of Ag_2O with the carboxylic acid. At this stage two pathways are possible. In path A, **LXI** undergoes decarboxylation to form aryl-Ag(I) **LXII**. Transmetalation of **LXII** with the Au(I) chloride salt, with the concomitant formation of AgCl, would afford the aryl-Au(I). On the other hand, in path B **LXI** undergoes ligand exchange with the Au(I) chloride salt to form the Au(I) carboxylate **LXIII**. Subsequent decarboxylation of **LXIII** would afford the aryl-Au(I) product. The latter hypothesis is supported by the fact that Au(I)-carboxylates are generally prepared from the corresponding Ag(I) salts.[92]

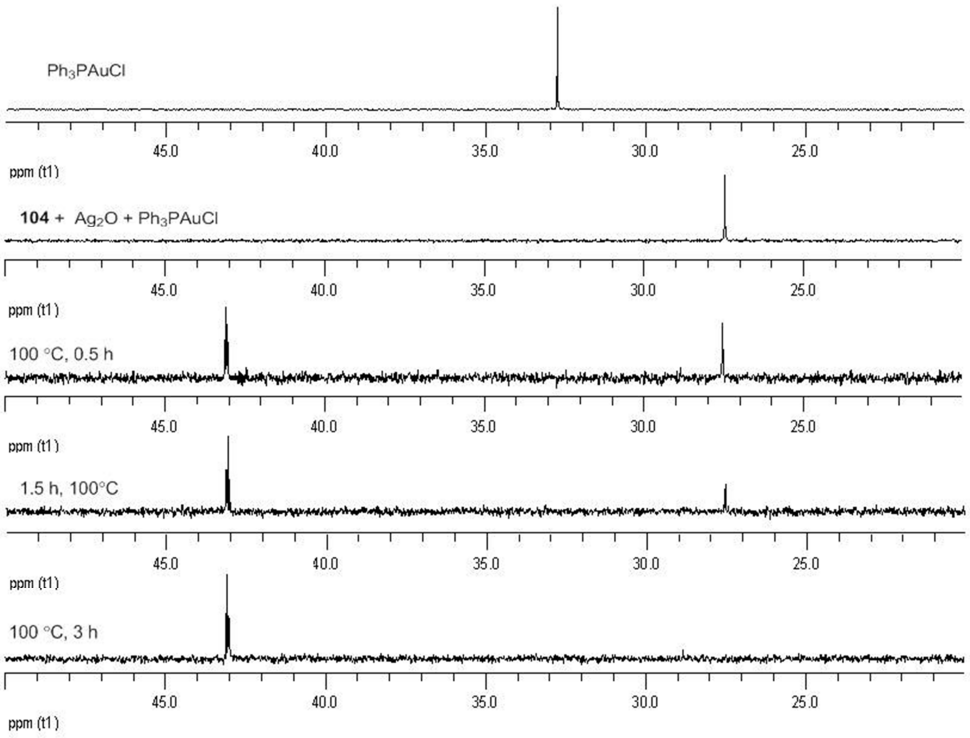
In order to determine the identity of the different species involved when using these conditions, the reaction of benzoic acid **104** with Ph_3PAuCl (**109**) and Ag_2O was followed by ^1H and ^{31}P NMR spectroscopy. The results are outlined in Scheme 135, 136 and 137.



Scheme 135. Decarboxylative auration of **115**.



Scheme 136. ^{1}H NMR study of the reaction corresponding to the auration of **104** with **109**.



Scheme 137. ^{31}P NMR study of the reaction corresponding to the auration of **104** with **109**.

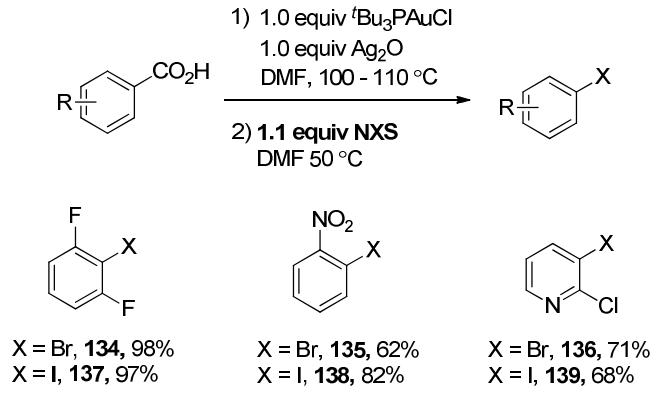
Stirring **104** and Ag_2O in DMF at 50 °C for 5 minutes afforded quantitative formation of the corresponding Ag(I)-carboxylate **132** (Scheme 136, A). After addition of Ph_3PAuCl, a small change was observed by ^{1}H NMR (Scheme 136, B) while ^{31}P NMR indicated complete conversion of Ph_3PAuCl (32.7 ppm) to species assigned as Au(I)-carboxylate **133** (28.5 ppm). Upon heating of **133** at 100 °C for 3 h, clean conversion to **115** was observed by ^{1}H (Scheme 136, C, D and E) and ^{31}P NMR (43.0 ppm, Scheme 137). These observations are consistent with Au(I) mediating the decarboxylation of **104** even in the presence of Ag(I) salts (path *b* in Scheme 134).

6.6. Synthetic applications of the decarboxylative auration of arenes

Aryl- and alkenyl-Au(I) complexes have recently been shown to undergo a variety of transformations, including halogenations and Pd-catalysed cross-couplings, which could be combined with this new decarboxylative auration protocol.[93] In order to demonstrate the potential of this new entry point to aryl-Au(I) complexes, we

explored the possibility of a one-pot transformation, from benzoic acids to haloarenes, in a process that is reminiscent of the Hunsdiecker reaction. However, the standard version of this transformation does not proceed satisfactorily with aromatic carboxylic acids, having a very limited substrate scope and low reproducibility.[94]

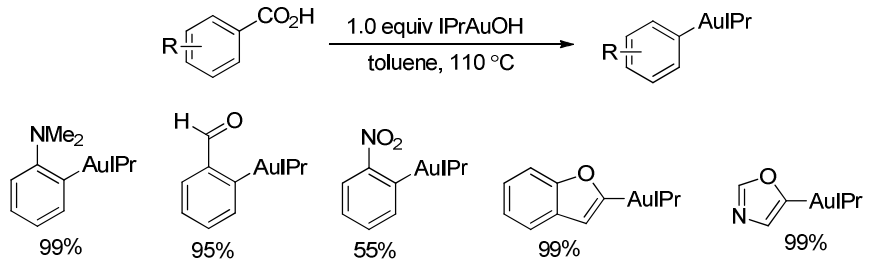
To this end, a one-pot process for the halogenation of aryl-Au(I) complexes was attempted. The addition of 1.1 equiv of NBS or NIS after the decarboxylative auration afforded the brominated compounds **134**, **135** and **136**, and the iodinated compounds **137**, **138** and **139** in excellent yields (Scheme 138). These results indicate that Au(I)-mediated decarboxylation could be used to develop a general methodology for the halogenation of arenes.



Scheme 138. One-pot procedure for the decarboxylative halogenation of (hetero)aromatic carboxylic acids. Yields were determined by ^{1}H NMR using mesitylene as an internal standard.

6.7. Concurrent work by other research groups

Nolan and co-workers reported a similar protocol for the decarboxylative auration of arenes.[95] The authors make use of a basic Au(I) species (IPrAuOH) bearing an N-heterocyclic carbene as a ligand. The protocol allows the auration of carboxylic acids bearing an *ortho* electron-withdrawing or -donating substituent, or an α heteroatom (Scheme 139).



Scheme 139. Nolan's decarboxylative auration of (hetero)aromatic carboxylic acids.

6.8. Conclusion

A novel mode of reactivity for Au(I), which provides access to a variety of aryl-Au(I) substrates from cheap and readily available carboxylic acids has been demonstrated. The decarboxylation process occurs at very low temperatures (50 – 80 ºC), a remarkable achievement when compared with high temperature protocols mediated by Ag(I) or Cu(I). In addition, the greater stability of aryl-Au(I) towards protodemetallation as compared to aryl-Ag(I) and -Cu(I) is demonstrated by the possibility of isolating and characterising these organometallic compounds.

It has also been demonstrated that these complexes can be used for synthetic applications. Hence, a one-pot procedure for the formation of iodo- and bromo-arenes in good yields was accomplished.

Although it has been proven that Au(I) salts are capable of decarboxylating benzoic acids, work must be performed in this area for its application in organic synthesis:

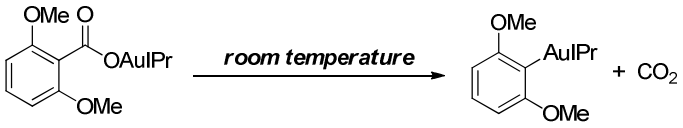
- This chapter presents the possibility of activating C−CO_2H bonds using stoichiometric amounts of Au(I). Therefore, a catalytic version of this decarboxylative protocol is greatly needed to minimise the cost efficiency of this transformation.
- It has been demonstrated that the nature of the ligand in the Au(I) salt plays an important role on the decarboxylation step. Therefore, a fine tuning of this ligand would probably allow the decarboxylation to occur at lower temperatures, allowing low-temperature decarboxylative transformations in the future.

Chapter 7. General conclusions and future work

In this thesis we have demonstrated that benzoic acids are potentially useful synthons in organic synthesis that can be used in many synthetic transformations. However, as mentioned in the conclusions of each chapter, the early stages of decarboxylative transformations place this strategy far from industrial applications. Future work must be undertaken in order to position decarboxylative methodologies as versatile and useful industrial tools.

A decrease in the decarboxylation temperatures is of high priority in order that the processes may tolerate sensitive functional groups. In chapter 6, we have demonstrated that Au(I) salts are able to mediate the activation of C−CO_2H. This Au(I)-mediated decarboxylation affords stable aryl-Au(I) complexes that do not lead to protodecarboxylation byproducts. On the other hand, we showed that aryl-Ag(I) complexes are very reactive, leading to protodemetalation or even radical based byproducts.

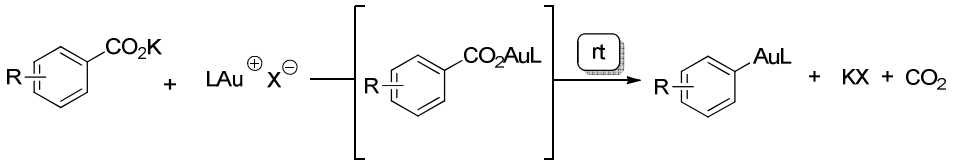
Recently, Wendt, Ahlquist and co-workers, reported a computational study on the decarboxylation of Au(I) carboxylates.[96] The authors suggest that it should be possible to decarboxylate 2,6-dimethoxybenzoic acid with IPrAu(I) complex at room temperature (Scheme 140). Although this is a theoretical result, it encourages chemists in the search for a highly desirable room temperature decarboxylation step.



Scheme 140. Room temperature decarboxylative auration of 2,6-dimethoxybenzoic acid.

In chapter 6, it has also been proven that the ligand at the Au(I) centre has a tremendous impact on the decarboxylation step. Therefore, a thorough screen of different ligands, including all types of phosphines or N-heterocyclic carbenes should be carried out (Scheme 141). Building upon this theoretical observation, the great

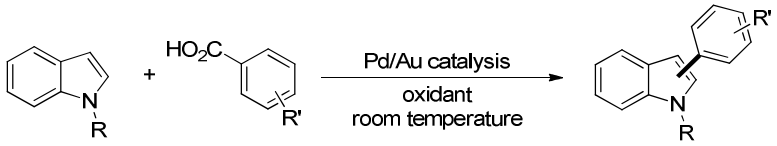
diversity of structurally and electronically varied phosphines and N-heterocyclic carbenes present in the literature should allow identification of a ligand that facilitates this decarboxylation process to occur at much lower temperatures.[97]



Scheme 141. Decarboxylative auration at room temperature.

Thus far, only benzoic acids bearing electron-withdrawing or donating groups in *ortho* as well as α–heteroatom carboxylic acids are suitable for the Au(I)-mediated decarboxylation. However, Nolan and co-workers reported excellent yields on the decarboxylative auration of styrene carboxylic acid and 4-methoxybenzoic acid.[95] These results suggest that fine tuning of the ligand of the Au centre may lead to decarboxylation of benzoic acids, regardless of their substitution pattern.

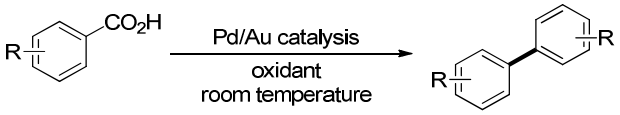
If the aforementioned studies on the Au(I)-mediated decarboxylation at low temperatures are successful, the next step would be to apply this low temperature decarboxylative activation process to synthetically useful transformations. Several reports have shown the possibility of combining Au(I) and Pd(II) as complementary catalysts.[93] Our research group has demonstrated the possibility of indole arylation at room temperature using iodoarenes as coupling partners.[51] Therefore, a methodology that uses a Pd(II)/Au(I) catalytic system for the decarboxylative C−H arylation of indoles at room temperature may be envisaged (Scheme 142).



Scheme 142. Room temperature Pd/Au-catalysed decarboxylative arylation of indoles.

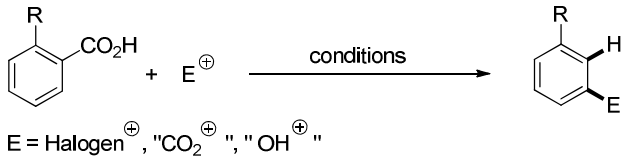
In this case, an external oxidant would be needed, to reoxidise the Pd(0) to Pd(II). This would ideally be performed by oxygen.[98]

In the same vein, a dimerisation of aromatic carboxylic acids, catalysed by Pd(II)/Au(I), could also be envisaged (Scheme 143).



Scheme 143. Room temperature Pd/Au-catalysed decarboxylative homocoupling of benzoic acids.

Another possible project in the near future would involve the extension of our work on the formal *meta*-selective functionalisation of arenes to other transformations. Benzoic acids have been shown to be efficient *ortho*-directing groups for a wide variety of transformations (chapter 3). Therefore, it should be possible to develop a methodology that allows the use of benzoic acids as traceless directing groups for example, for the formal *meta*-halogenation, -carboxylation or -hydroxylation (Scheme 144).



Scheme 144. Benzoic acids for the formal *meta*-functionalisation of arenes.

Although the *meta*-halogenation has been successfully developed by Hartwig and co-workers, it involves a two-step borylation/halogenation process and the use of expensive Ir salts as catalysts.[99] Therefore, a cheaper one-pot procedure for this transformation is highly required.

Thus far, no examples of a *meta*-selective direct C−H carboxylation or hydroxylation procedures are reported. Therefore, the application of our strategy to these substrates to obtain the *meta* functionalised arenes would be highly desirable.

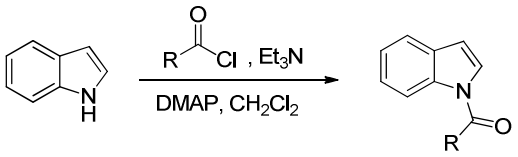
Chapter 8. Experimental

8.1. General remarks

All reagents were purchased from Aldrich, Acros, Alfa-Aesar, Merk, Fluka, Strem or Maybridge and were used without further purification unless otherwise stated. Solvents were obtained anhydrous from a MBraun MB SPS-800 solvent purification system. Thin-layer chromatography analyses (TLC) were carried out on analytical silica gel plates (0.25 mm, F_{254}, Merck). Column chromatography was carried under low pressure (flash) conditions, using silica gel 60 (0.040–0.063 mm particle size) (Merck). The TLC's were analyzed by UV (254 nm) and stained with *p*-anisaldehyde or $KMnO_4$. R_f values described are approximate. Melting points (mp) were determined with a Gallenkamp apparatus and are uncorrected. Infrared spectra (IR) were recorded with a Bruker Tensor 37 FTIR machine. Representative frequencies are given in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker 400 and normalised on the signal of tetramethylsilane (TMS) and $CDCl_3$ respectively. Chemical shifts are given in δ (ppm) and coupling constant values (*J*) are given in Hz. The following abbreviations are employed for the multiplicities: s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, hept = heptuplet, m = multiplet (and their corresponding combinations). The solvent used is indicated for each case. Gas Chromatography-Mass Spectrometry (GCMS) was performed using a Varian 450 GC coupled with a Varian 200 MS and using Helium as a carrier gas. High resolution mass spectra were recorded by the EPSRC National Mass Spectrometry Service Center in Swansea (UK). Atomic Absorption Spectroscopy (AAS) was carried out in a Varian 220FS apparatus. X-ray structures were obtained by Professor A. M. Z. Slawin, University of Glasgow, Scotland.

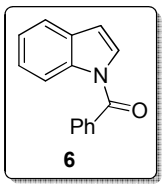
8.2. Experimental Chapter 2

8.2.1. General procedure for the synthesis of *N*-carbonyl indoles



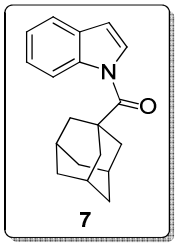
Acyl chloride (1.17 equiv) was added dropwise to a solution of indole (1.0 equiv), DMAP (0.1 equiv) and triethylamine (1.48 equiv) in anhydrous CH_2Cl_2 (0.6 M) at 0 ºC. The solution was warmed up to room temperature and stirred for 16 h. After this time, the reaction mixture was evaporated to dryness under reduced pressure. The crude was portioned between Et_2O and saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude was purified by column chromatography to afford the desired *N*-carbonyl indoles.

8.2.1.1. N-Benzoylindole[100]



The reaction was performed following the general procedure with benzoyl chloride (0.54 mL, 4.68 mmol), indole (468 mg, 4.0 mmol), DMAP (48.8 mg, 0.4 mmol), triethylamine (0.824 mL, 5.92 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **6** as a white solid (851 mg, 96%). R_f 0.40 (hexanes:EtOAc 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, 1H, J = 8.3 Hz), 7.74 – 7.72 (m, 2H), 7.52 (t, 2H, J = 7.4 Hz), 7.38 (m, 1H), 7.33 – 7.28 (m, 2H), 6.61 (dd, 1H, J = 3.8, 0.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 136.1, 134.7, 131.9, 130.8, 129.2, 128.6, 127.6, 124.9, 124.0, 120.9, 116.4, 108.6.

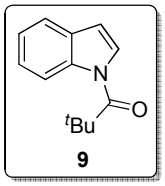
8.2.1.2. N-(1-Adamantanecarbonyl)indole



7

The reaction was performed following the general procedure with 1-adamantanecarbonyl chloride (2.3 mL, 11.7 mmol), indole (1.17 g, 10 mmol), DMAP (122 mg, 1 mmol), triethylamine (2.06 mL, 14.8 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **7** as a white solid (1.83 g, 96%). m.p. 135−137 ºC; R_f 0.22 (hexanes:EtOAc 98:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 9.1 Hz); 7.85 (d, 1H, *J* = 4.0 Hz), 7.47 (d, 1H, *J* = 9.1 Hz), 7.16 – 7.28 (m, 2H), 6.53 (d, 1H, *J* = 4.0 Hz), 2.17 – 2.15 (m, 6H), 2.08 (m, 3H), 1.76 – 1.74 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 136.8, 129.2, 125.6, 125.0, 123.4, 120.4, 117.4, 107.9, 44.2, 39.6, 38.3, 28.3; HRMS (EI) calcd. $C_{13}H_{14}BrNO$: (M^+), 279.1623; found: (M^+), 279.1627.

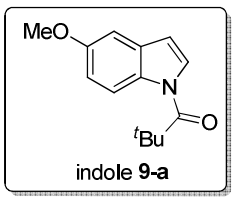
8.2.1.3. N-Pivaloylindole[101]



9

The reaction was performed following the general procedure with pivaloyl chloride (4.3 mL, 35.1 mmol), indole (3.51 g, 30.0 mmol), DMAP (0.366 g, 3.00 mmol), triethylamine (6.2 mL, 44.4 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **9** as a white solid (5.79 g, 96%). R_f 0.41 (hexanes:EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, 1H, *J* = 8.4 Hz), 7.73 (d, 1H, *J* = 3.8 Hz), 7.56 (d, 1H, *J* = 7.6 Hz), 7.37 – 7.33 (m, 1H), 7.28 – 7.24 (m, 1H), 6.62 (d, 1H, *J* = 3.8 Hz), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 137.2, 129.8, 126.1, 125.5, 123.9, 120.9, 117.6, 108.6, 41.6, 29.1.

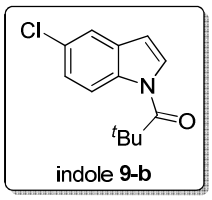
8.2.1.4. N-Pivaloyl-5-methoxyindole[101]



indole **9-a**

The reaction was performed following the general procedure with pivaloyl chloride (0.144 mL, 1.17 mmol), 5-methoxyindole (0.147 g, 1.00 mmol), DMAP (0.012 g, 0.10 mmol), triethylamine (0.206 mL, 1.48 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **9-a** as a white solid (0.218 g, 94%). R_f 0.20 (hexanes:EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 9.0 Hz), 7.72 (d, 1H, *J* = 3.8 Hz), 7.03 (d, 1H, *J* = 2.6 Hz), 6.96 (dd, 1H, *J* = 9.0, 2.6 Hz), 6.56 (d, 1H, *J* = 3.8 Hz), 3.87 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 156.8, 131.9, 130.7, 126.7, 118.5, 113.8, 108.5, 103.7, 56.1, 41.5, 29.2.

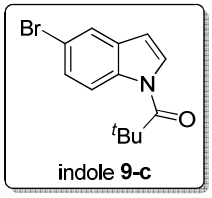
8.2.1.5. N-Pivaloyl-5-chloroindole[101]



indole **9-b**

The reaction was performed following the general procedure with pivaloyl chloride (0.29 mL, 2.34 mmol), 5-chloroindole (0.303 g, 2.00 mmol), DMAP (0.024 g, 0.20 mmol), triethylamine (0.41 mL, 2.96 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **9-b** as a white solid (0.409 g, 87%). R_f 0.38 (hexanes:EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, *J* = 8.9 Hz), 7.76 (d, 1H, *J* = 3.8 Hz), 7.53 (d, 1H, *J* = 2.1 Hz), 7.30 (dd, 1H, *J* = 8.9, 2.1 Hz), 6.57 (d, 1H, *J* = 3.8 Hz), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.3, 135.5, 131.0, 129.4, 127.2, 125.6, 120.5, 118.7, 107.9, 41.6, 29.0.

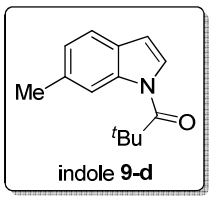
8.2.1.6. N-Pivaloyl-5-bromoindole



indole **9-c**

The reaction was performed following the general procedure with pivaloyl chloride (0.29 mL, 2.34 mmol), 5-bromoindole (0.392 g, 2.00 mmol), DMAP (0.024 g, 0.20 mmol), triethylamine (0.41 mL, 2.96 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **9-c** as a white solid (0.497 g, 89%). m.p. 120–122 ºC; R_f 0.35 (hexanes:EtOAc 95:5); IR: 1686, 1436, 1302, 1183; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, 1H, *J* = 8.7 Hz), 7.75 (d, 1H, *J* = 3.8 Hz), 7.69 (d, 1H, *J* = 2.0 Hz), 7.44 (dd, 1H, *J* = 8.7, 2.0 Hz), 6.57 (d, 1H, *J* = 3.8 Hz), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 135.9, 131.5, 128.3, 127.1, 123.5, 119.1, 117.1, 107.7, 41.6, 29.0. HRMS (EI) calcd. $C_{13}H_{14}BrNO$: (M^+), 279.0259; found: (M^+), 279.0254.

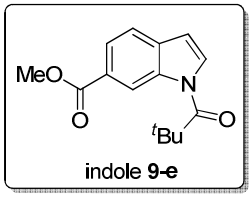
8.2.1.7. N-Pivaloyl-6-methylindole[101]



indole **9-d**

The reaction was performed following the general procedure with pivaloyl chloride (0.14 mL, 1.17 mmol), 6-methylindole (0.131 g, 1.00 mmol), DMAP (0.012 g, 0.1 mmol), triethylamine (0.21 mL, 1.48 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **9-d** as a colorless oil (0.180 g, 84%). R_f 0.53 (hexanes:EtOAc 96:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 0.5 Hz), 7.68 (d, 1H, *J* = 3.8 Hz), 7.46 (d, 1H, *J* = 7.9 Hz), 7.36 – 7.04 (m, 1H), 6.59 (d, 1H, *J* = 3.8 Hz), 2.52 (s, 3H), 1.54 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 137.2, 135.2, 127.1, 125.1, 125.0, 120.0, 117.6, 108.2, 41.2, 28.7, 22.0.

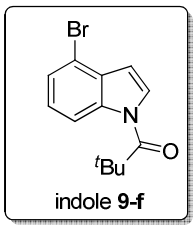
8.2.1.8. N-Pivaloyl-6-methoxycarbonylindole[101]



indole **9-e**

The reaction was performed following the general procedure with pivaloyl chloride (0.28 mL, 2.34 mmol), 6-methoxycarbonylindole (0.294 g, 2.00 mmol), DMAP (0.024 g, 0.20 mmol), triethylamine (0.41 mL, 2.96 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 90:10) to afford **9-e** as a white solid (0.497 g, 96%). R_f 0.24 (hexanes:EtOAc 95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, 1H, *J* = 1.4 Hz), 7.99 (dd, 1H, *J* = 8.2, 1.4 Hz), 7.89 (d, 1H, *J* = 3.8 Hz), 7.60 (d, 1H, *J* = 8.2 Hz), 6.67 (d, 1H, *J* = 3.8 Hz), 3.95 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 168.1, 136.6, 133.4, 128.8, 127.2, 125.6, 120.6, 119.5, 108.4, 52.4, 41.7, 29.0.

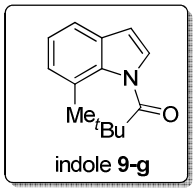
8.2.1.9. N-Pivaloyl-4-bromoindole



indole **9-f**

The reaction was performed following the general procedure with pivaloyl chloride (0.28 mL, 2.34 mmol), 4-bromoindole (0.390 g, 2.00 mmol), DMAP (0.024 g, 0.20 mmol), triethylamine (0.41 mL, 2.96 mmol). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **9-f** as a white solid (0.499 g, 89%). m.p. 61–63 ºC; R_f 0.37 (hexanes:EtOAc 95:5); IR: 1690, 1415, 1308, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 1H, *J* = 8.1 Hz), 7.80 (d, 1H, *J* = 3.6 Hz), 7.44 (d, 1H, *J* = 8.1 Hz), 7.21 (t, 1H, *J* = 8.1 Hz), 6.71 (d, 1H, *J* = 3.6 Hz), 1.53 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 137.1, 130.1, 126.5, 126.2, 126.1, 116.3, 114.4, 108.0, 41.1, 28.6; MS (EI) *m/z* 281 (M^+, 100), 279 (M^+, 100).

8.2.1.10. N-Pivaloyl-7-methylindole[102]



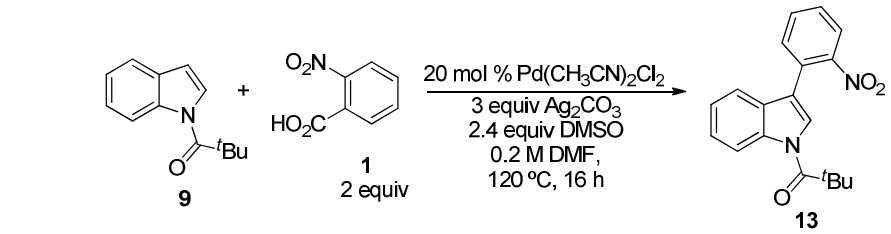
A solution of 7-methylindole (0.150 g, 1.14 mmol) in anhydrous THF (2.5 mL) was added to a mixture of KH (0.291 g of a 30–35% w/w suspension in mineral oil, washed with hexanes) in anhydrous THF (2.5 mL) at 0 ºC. After 5 min, the mixture was warmed up to room temperature and after 40 min, pivaloyl chloride (0.165 mL, 1.34 mmol) was added to the resulting mixture. After 16 h, the reaction was quenched with a saturated solution of $NaHCO_3$ (6 mL). The aqueous phase was extracted with EtOAc (5 mL) and the combined organic layers were washed with brine (2 × 5 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **9-g** as a colorless oil (0.202 g, 82%). R_f 0.75 (hexanes:EtOAc 95:5); IR: 1702, 1293, 1168; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 3.6 Hz), 7.48 (d, 1H, *J* = 7.6 Hz), 7.24 (t, 1H, *J* = 7.6 Hz), 7.16 (d, 1H, *J* = 7.6 Hz), 6.64 (d, 1H, *J* = 3.6 Hz), 2.39 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 136.2, 130.7, 127.2, 125.8, 125.6, 123.4, 118.5, 107.3, 42.0, 29.2, 21.5; MS (EI) *m/z* 215 (M^+, 100).

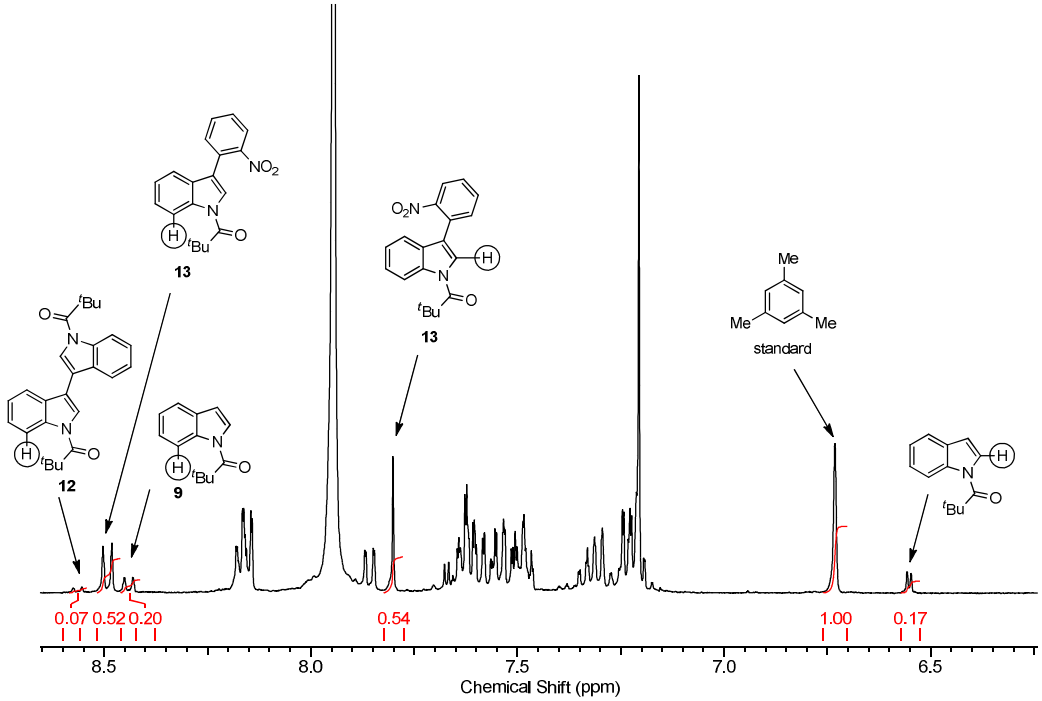
8.2.2. Optimisation of the decarboxylative C−H arylation of indoles

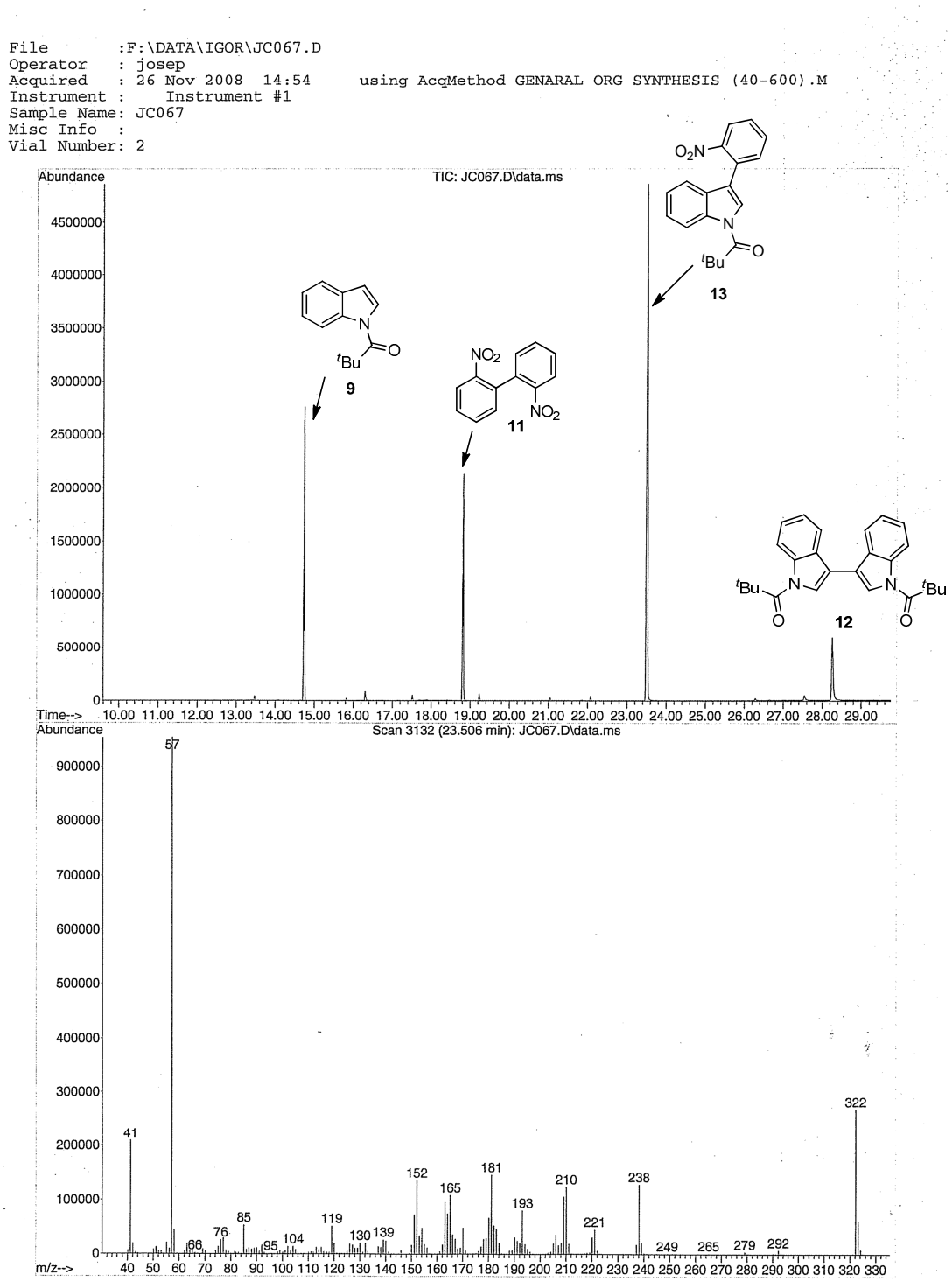
8.2.2.1. Initial procedure for decarboxylative C−H arylation of indoles

N-pivaloyl indole (**9**) (25.1 mg, 0.125 mmol), 2-nitrobenzoic acid (**1**) (20.9 mg, 0.25 mmol), Ag_2CO_3 (104 mg, 0.375 mmol) and $Pd(TFA)_2$ (8.3 mg, 0.025 mmol) in 0.625 mL of DMF:DMSO (95:5) was heated at 120 ºC for 16 h. After this time, the solution was filtered through a plug of SiO_2 and flushed with EtOAc. The solvent was evaporated to dryness and mesitylene (1 mL of 0.042 M in $CDCl_3$, 0.042 mmol) was added. The crude was then analysed by ^{1}H NMR and GCMS.

A ^{1}H NMR and GCMS of the crude for reaction in Table 6, entry 2 (page 65) is shown below.


20 mol % Pd(CH3CN)2Cl2
3 equiv Ag2CO3
2.4 equiv DMSO
0.2 M DMF,
120 °C, 16 h
9
1
2 equiv
13


13
12
9
13
standard
0.07
0.52
0.20
0.54
1.00
0.17
8.5
8.0
7.5
7.0
6.5
Chemical Shift (ppm)



This reaction afforded 52% of product **13**, 20% of starting material and approximately 4% of C3-C3 indole coupling dimer. As shown in the GCMS spectra, the formation of biaryl **11** was also observed.

8.2.2.2. Effect of the protecting group at the nitrogen of the indole

The reactions were carried out following the general procedure described in section 8.2.2.1 but using N-protected indoles described in Table 1.

8.2.2.3. Effect of the solvent

The reactions were carried out following the general procedure described in section 8.2.2.1 adding the solvent or solvent mixture described in Table 2.

8.2.2.4. Effect of the equivalents of DMSO

The reactions were carried out following the general procedure described in section 8.2.2.1 adding different equivalents of DMSO as described in Table 3.

8.2.2.5. Re-optimised protocol for the decarboxylative C−H arylation of indoles

N-pivaloyl indole (**9**) (25.1 mg, 0.125 mmol), 2-nitrobenzoic acid (**1**) (20.9 mg, 0.25 mmol), Ag_2CO_3 (104 mg, 0.375 mmol) and $Pd(TFA)_2$ (8.3 mg, 0.025 mmol), DMSO (21.3 μL, 0.3 mmol) in 0.625 mL of DMF was heated at 120 ºC for 16 h. After this time, the solution was filtered through a plug of SiO_2 and flushed with EtOAc. The solvent was evaporated to dryness and mesitylene (1 mL of 0.04 M in $CDCl_3$, 0.04 mmol) was added. The crude was then analysed by ^{1}H NMR and GCMS.

8.2.2.6. Effect of the Ag salt

The reactions were carried out following the general procedure described in section 8.2.2.4 adding different Ag(I) salts as described in Table 4.

8.2.2.7. Effect of the temperature

The reactions were carried out following the general procedure described in section 8.2.2.2 using $Pd(CH_3CN)_2Cl_2$ (6.4 mg, 0.025 mmol) as catalyst and at the temperatures described in Table 5.

8.2.2.8. Effect of the concentration

The reactions were carried out following the general procedure described in section 8.2.2.2 using $Pd(CH_3CN)_2Cl_2$ (6.4 mg, 0.025 mmol) at different concentrations of DMF as described in Table 6.

8.2.2.9. Effect of the radical scavengers

The reactions were carried out following the general procedure described in section 8.2.2.2 using $Pd(CH_3CN)_2Cl_2$ (6.4 mg, 0.025 mmol), 4,5-dimethoxy-2-nitrobenzoic acid (**14**) (56.8 mg, 0.25 mmol) and radical scanvengers described in Table 7.

8.2.2.10. Experiments for the protodecarboxylation of 2-nitrobenzoic acid (10)

8.2.2.10.1. Protodecarboxylation with $Pd(TFA)_2$

The reaction was carried out using 2-nitrobenzoic acid (**1**) (41.2 mg, 0.25 mmol), $Pd(TFA)_2$ (64 mg, 0.25 mmol) and DMSO (21 μL, 0.6 mmol) in 0.625 mL of DMF at 120 ºC for 16 h. After this time, the solution was filtered through a plug of SiO_2 and flushed with EtOAc. The solvent was evaporated to dryness and mesitylene (1 mL of 0.04 M in $CDCl_3$, 0.04 mmol) was added. The crude was then analysed by ^1H NMR and GCMS.

8.2.2.10.2. Protodecarboxylation with Ag_2CO_3

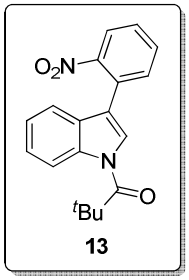
The reaction was carried out using 2-nitrobenzoic acid (**1**) (41.2 mg, 0.25 mmol), Ag_2CO_3 (103 mg, 0.375 mmol) and DMSO (21 μL, 0.6 mmol) in 0.625 mL of DMF at 120 ºC for 16 h. After this time, the solution was filtered through a plug of SiO_2 and flushed with EtOAc. The solvent was evaporated to dryness and mesitylene (1 mL of 0.04 M in $CDCl_3$, 0.04 mmol) was added. The crude was then analysed by ^1H NMR and GCMS.

8.2.3. Optimised procedure for C3 decarboxylative C–H arylation of N-pivaloylindoles with benzoic acids

A mixture of $Pd(MeCN)_2Cl_2$ (0.2 equiv), *N*-pivaloylindole (1 equiv), the benzoic acid (2 equiv), Ag_2CO_3 (3 equiv) and DMSO (2.4 equiv) in DMF (0.1 M) was stirred at

110 ºC for 16 hours. After this time, the reaction mixture was cooled down to room temperature, filtered through a plug of silica gel and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography to afford the desired C3 arylated product.

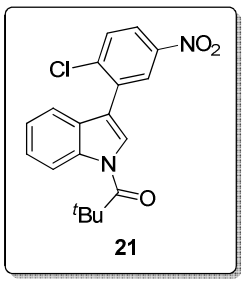
8.2.3.1. 3-(2'-Nitrophenyl)-N-pivaloyindole



13

The reaction was performed following the general procedure with $Pd(TFA)_2$ (0.033 g, 0.10 mmol), **9** (0.100 g, 0.5 mmol), 2-nitrobenzoic acid (0.167 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (2.5 mL, 0.2 M) at 120 ºC. The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **13** as a yellow solid (0.101 g, 63%). m.p. 145–146 ºC; R_f 0.18 (hexanes:EtOAc 95:5); IR: 1694, 1523, 1348; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, 1H, *J* = 8.4 Hz), 7.93 (d, 1H, *J* = 8.1 Hz), 7.88 (s, 1H), 7.71 – 7.64 (m, 2H), 7.58 – 7.53 (m, 2H), 7.44 – 7.37 (m, 1H), 7.32 – 7.26 (m, 1H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 150.1, 136.8, 132.5, 132.2, 128.5, 128.2, 127.4, 125.8, 124.5, 124.2, 124.0, 118.7, 117.6, 117.3, 41.4, 28.7; HRMS (EI) calcd. $C_{19}H_{18}N_2O_3$: (M^+), 322.1317; found: (M^+), 322.1314.

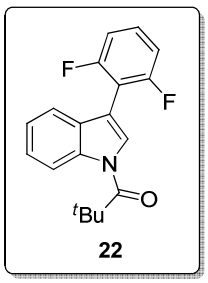
8.2.3.2. 3-(2'-Chloro-5'-nitrophenyl)-N-pivaloylindole



21

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9** (0.100 g, 0.50 mmol), 2-chloro-5-nitrobenzoic acid (0.201 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (5 mL). The crude product was purified by column chromatography (hexanes:EtOAc:CH_2Cl_2 94:1:5) to afford **21** as a white solid (0.136 g, 76%). m.p. 124–125 ºC; R_f 0.37 (hexanes:CH_2Cl_2:EtOAc 85:14:1); IR: 1683, 1521, 1343; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, 1H, *J* = 8.4 Hz), 8.47 (d, 1H, *J* = 2.7 Hz), 8.20 (dd, 1H, *J* = 8.8, 2.7 Hz), 8.04 (s, 1H), 7.75 (d, 1H, *J* = 8.8 Hz), 7.52 (d, 1H, *J* = 7.8 Hz), 7.45 (dd, 1H, *J* = 11.4, 4.2 Hz), 7.40 – 7.32 (m, 1H), 1.58 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 146.7, 140.3, 136.7, 133.7, 131.3, 127.7, 126.4, 125.9, 125.7, 124.2, 123.2, 119.1, 117.7, 117.3, 41.5, 28.7. HRMS (EI) calcd. $C_{19}H_{17}ClN_2O_3$: (M^+), 356.0926; found: (M^+), 356.0925.

8.2.3.3. 3-(2',6'-Difluorophenyl)-N-pivaloylindole

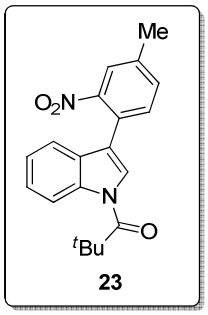


22

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9** (0.100 g, 0.5 mmol), 2,6-difluorobenzoic acid (0.237 g, 1.5 mmol), Ag_2CO_3 (0.620 g, 2.25 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (1.25 mL, 0.4 M) for 3 h. The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **22** as a white solid (0.110 g, 70%). m.p. 138–139 ºC;

R_f 0.36 (hexanes:EtOAc 98:2); IR: 1691, 1449, 1349; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, 1H, *J* = 8.4 Hz), 7.94 (s, 1H), 7.48 (dd, 1H, *J* = 8.4, 1.4 Hz), 7.43 − 7.29 (m, 3H), 7.09 − 7.03 (m, 2H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 160.7 (dd, 2C, *J* = 249.0, 6.9 Hz), 136.8, 129.2 (t, *J* = 10.2 Hz), 128.22, 126.2, 125.4, 123.7, 120.21 (t, *J* = 3.1 Hz), 117.3, 111.8 (dd, *J* = 19.6, 6.4 HZ), 110.6 (t, *J* = 19.6 Hz), 109.6, 41.4, 28.7. HRMS (EI) calcd. $C_{19}H_{17}F_2NO$: (M^+), 313.1278; found: (M^+), 313.1272.

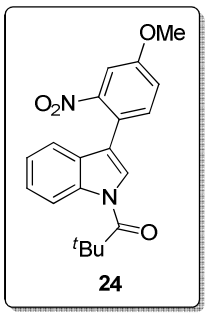
8.2.3.4. 3-(4'-Methyl-2'-nitrophenyl)-N-pivaloylindole



23

The reaction was performed following the general procedure with $Pd(TFA)_2$ (0.033 g, 0.10 mmol), **9** (0.100 g, 0.5 mmol), 4-methyl-2-nitrobenzoic acid (0.181 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (2.5 mL, 0.2 M) at 120 ºC. The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **23** as a yellow solid (0.096 g, 57%). m.p. 110–111 ºC; R_f 0.18 (hexanes:EtOAc 98:2); IR: 1682, 1526, 1345; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, 1H, *J* = 8.4 Hz), 7.76 (s, 1H), 7.66 (s, 1H), 7.44 – 7.38 (m, 2H), 7.33 – 7.27 (m, 2H), 7.22 – 7.16 (m, 1H), 2.43 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 149.8, 139.2, 136.8, 133.1, 132.2, 128.4, 125.7, 124.5, 124.3, 123.9, 118.7, 117.6, 117.3, 41.3, 28.7, 21.0; HRMS (EI) calcd. $C_{20}H_{20}N_2O_3$: (M^+), 336.1474; found: (M^+), 336.1475.

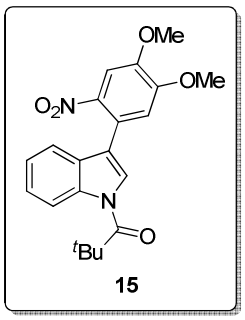
8.2.3.5. 3-(4'-Methoxy-2'-nitrophenyl)-N-pivaloylindole



24

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9** (0.100 g, 0.5 mmol), 4-methoxy-2-nitrobenzoic acid (0.197 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (2.5 mL, 0.2 M). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **24** as a yellow solid (0.103 g, 57%). m.p. 119−121 ºC. R_f 0.22 (hexanes:EtOAc 90:10); IR: 1692, 1531, 1352, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, 1H, J = 8.4 Hz), 7.74 (s, 1H); 7.44 (d, 1H, J = 8.4 Hz), 7.36 (d, 1H, J = 2.3 Hz), 7.33 − 7.25 (m, 2H), 7.22 − 7.16 (m, 1H), 7.14 (dd, 1H, J = 8.5, 2.6 Hz), 3.85 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 159.8, 150.8, 137.1, 133.8, 128.9, 126.0, 124.6, 124.3, 119.7, 119.2, 119.0, 117.9, 117.6, 109.5, 56.4, 41.7, 29.0. HRMS (EI) calcd. $C_{20}H_{20}N_2O_4$: (M^+), 352.1423; found: (M^+) 352.1419.

8.2.3.6. 3-(4',5'-Dimethoxy-2'-nitro)-N-pivaloylindole

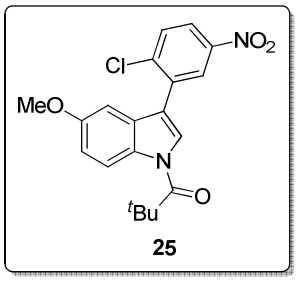


15

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9** (0.100 g, 0.5 mmol), 4,5-dimethoxy-2-nitrobenzoic acid (0.227 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (1.25 mL, 0.4 M). The crude product was purified by column chromatography (hexanes:EtOAc 70:30) to afford **15** as a yellow solid (0.084 g, 44%). m.p. 221−222

ºC; R_f 0.15 (hexanes:EtOAc 90:10); IR: 1693, 1509, 1321; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, 1H, *J* = 8.4 Hz), 7.85 (s, 1H), 7.64 (s, 1H), 7.42 – 7.38 (m, 1H), 7.34 – 7.26 (m, 2H), 6.97 (s, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 152.8, 148.8, 142.6, 137.1, 129.0, 126.0, 124.8, 124.4, 122.4, 119.1, 118.6, 118.0, 114.4, 108.4, 56.9 (2C), 41.8, 29.1; HRMS (EI) calcd. $C_{21}H_{22}N_2O_5$: (M^+), 382.1529; found: (M^+), 382.1520.

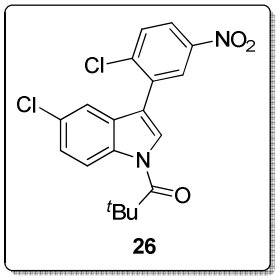
8.2.3.7. 3-(2'-Chloro-5'-nitrophenyl)-5-methoxy-N-pivaloylindole



25

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9-a** (0.115 g, 0.50 mmol), 2-chloro-5-nitrobenzoic acid (0.201 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (5 mL). The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **25** as a yellow solid (0.129 g, 67%). m.p. 173–174 ºC; R_f 0.23 (hexanes:EtOAc 95:5); IR: 1686, 1460, 1330; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, 1H, *J* = 9.1 Hz), 8.46 (d, 1H, *J* = 2.7 Hz), 8.20 (dd, 1H, *J* = 8.8, 2.7 Hz), 7.99 (s, 1H), 7.75 (d, 1H, *J* = 8.8 Hz), 7.05 (dd, 1H, *J* = 9.1, 2.5 Hz), 6.92 (d, 1H, *J* = 2.5 Hz), 3.84 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 156.9, 146.8, 140.4, 133.8, 131.4, 131.3, 128.6, 126.3, 126.2, 123.3, 118.5, 117.2, 114.3, 101.9, 55.7, 41.3, 28.9. HRMS (EI) calcd. $C_{20}H_{19}ClN_2O_4$: (M^+), 386.1033; found: (M^+), 386.1031.

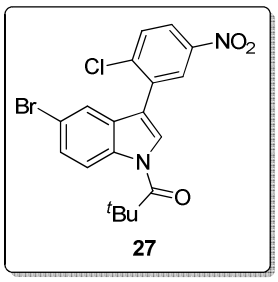
8.2.3.8. 3-(2'-Chloro-5'-nitrophenyl)-5-chloro-N-pivaloylindole



26

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.022 g, 0.086 mmol), **9-b** (0.102 g, 0.43 mmol), 2-chloro-5-nitrobenzoic acid (0.174 g, 0.87 mmol), Ag_2CO_3 (0.359 g, 1.3 mmol), DMSO (0.074 mL, 1.2 mmol) and DMF (4.3 mL). The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **26** as a white solid (0.120 g, 71%). m.p. 164–165 ºC; R_f 0.15 (hexanes:EtOAc 95:5) IR: 1700, 1520, 1342; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, 1H, *J* = 8.9 Hz), 8.40 (d, 1H, *J* = 2.6 Hz), 8.22 (dd, 1H, *J* = 8.8, 2.6 Hz), 8.03 (s, 1H), 7.75 (d, 1H, *J* = 8.8 Hz), 7.43 (d, 1H, *J* = 2.0 Hz), 7.39 (dd, 1H, *J* = 8.9, 2.0 Hz), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 146.7, 140.5, 135.1, 133.1, 131.3, 129.9, 128.9, 126.7, 126.3, 126.1, 123.7, 118.8, 118.7, 116.8, 41.5, 28.7; HRMS (EI) calcd. $C_{19}H_{16}Cl_2N_2O_3$: (M^+), 390.0538; found: (M^+), 390.0534.

8.2.3.9. 5-Bromo-3-(2'-chloro-5'-nitrophenyl)-N-pivaloylindole

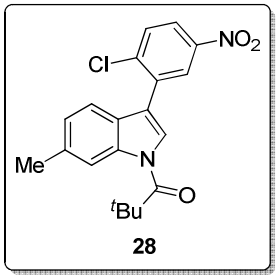


27

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9-c** (0.140 g, 0.50 mmol), 2-chloro-5-nitrobenzoic acid (0.201 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (5 mL). The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **27** as a white solid (0.140 g, 64%). m.p. 153–154 ºC; R_f 0.13 (hexanes:EtOAc 98:2); IR: 1704, 1524, 1346; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d,

1H, *J* = 8.9 Hz), 8.31 (d, 1H, *J* = 2.7 Hz), 8.14 (dd, 1H, *J* = 8.8, 2.7 Hz), 7.91 (s, 1H), 7.67 (d, 1H, *J* = 8.8 Hz), 7.50 (d, 1H, *J* = 1.8 Hz), 7.46 (dd, 1H, *J* = 8.9, 1.8 Hz), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 146.7, 140.5, 135.5, 133.1, 131.3, 129.5, 128.8, 126.5, 126.3, 123.7, 121.9, 119.1, 117.6, 116.7, 41.5, 28.7. HRMS (CI) calcd. $C_{19}H_{17}BrClN_2O_3$: ($[M+H]^+$), 435.0111; found: ($[M+H]^+$), 435.0106.

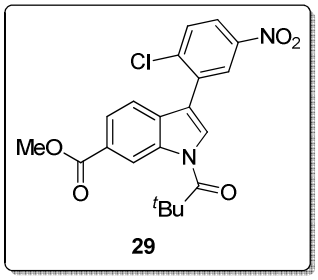
8.2.3.10. 3-(2'-Chloro-5'-nitrophenyl)-6-methyl-N-pivaloylindole



28

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9-d** (0.107 g, 0.50 mmol), 2-chloro-5-nitrobenzoic acid (0.201 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (5 mL). The crude product was purified by column chromatography (hexanes:EtOAc 97:3) to afford **28** as a yellow solid (0.137 g, 74%). m.p. 129–130 ºC; R_f 0.35 (hexanes:EtOAc 96:4); IR 1687, 1520, 1341; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.45 (m, 2H), 8.18 (dd, 1H, *J* = 8.8, 2.7 Hz), 7.98 (s, 1H), 7.73 (d, 1H, *J* = 8.8 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 7.19 (d, 1H, *J* = 7.8 Hz), 2.53 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 146.6, 140.3, 137.1, 136.2, 133.9, 131.3, 126.3, 125.6, 125.5, 125.2, 123.1, 118.7, 117.9, 117.3, 41.5, 28.7, 21.9. HRMS (EI) $C_{20}H_{19}ClN_2O_3$: (M^+), 370.1084; found: (M^+), 370.1089.

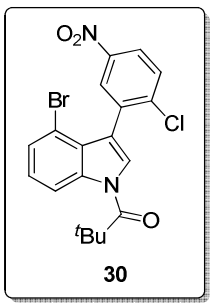
8.2.3.11. 3-(2'-Chloro-5'-nitrophenyl)-6-methoxycarbonyl-N-pivaloylindole



29

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.026 g, 0.10 mmol), **9-e** (0.130 g, 0.50 mmol), 2-chloro-5-nitrobenzoic acid (0.201 g, 1.0 mmol), Ag_2CO_3 (0.413 g, 1.5 mmol), DMSO (0.085 mL, 1.2 mmol) and DMF (5 mL). The crude product was purified by column chromatography (hexanes:EtOAc 95:5) to afford **29** as a yellow solid (0.137 g, 66%). m.p. 145–146 ºC; R_f 0.51 (hexanes:EtOAc 85:15); IR: 1729, 1694, 1522, 1320; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.43 (d, 1H, *J* = 2.7 Hz), 8.21 (dd, 1H, *J* = 8.8, 2.7 Hz), 8.16 (s, 1H), 8.05 (dd, 1H, *J* = 8.3, 1.4 Hz), 7.75 (d, 1H, *J* = 8.8 Hz), 7.53 (d, 1H, *J* = 8.3 Hz), 3.96 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 167.3, 146.7, 140.4, 136.2, 133.1, 131.4, 131.1, 128.3, 127.7, 126.4, 125.4, 123.6, 119.4, 118.9, 117.2, 52.2, 41.6, 28.7. HRMS (CI) calcd. $C_{21}H_{23}ClN_3O_5$: ($[M+NH_4]^+$), 432.1326; found: ($[M+NH_4]^+$), 432.1321.

8.2.3.12. 3-(2'-Chloro-5'-nitrophenyl)-4-bromo-N-pivaloylindole

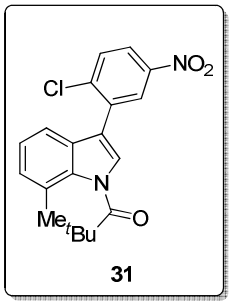


30

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (0.020 g, 0.076 mmol), **9-f** (0.108 g, 0.38 mmol), 2-chloro-5-nitrobenzoic acid (0.153 g, 0.76 mmol), Ag_2CO_3 (0.313 g, 1.14 mmol), DMSO (0.065 mL, 0.91 mmol) and DMF (3.8 mL). The crude product was purified by column chromatography (hexanes:CH_2Cl_2:EtOAc 90:9:1) to afford **30** as a white solid (0.073 g, 44%). R_f 0.41

(hexanes:CH_2Cl_2:EtOAc 80:19:1); IR 1696, 1522, 1345; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, 1H, *J* = 8.5 Hz), 8.33 (d, 1H, *J* = 2.4 Hz), 8.25 (dd, 1H, *J* = 8.5, 2.4 Hz), 7.80 (s, 1H), 7.66 (d, 1H, *J* = 8.8 Hz), 7.46 – 7.42 (m, 1H), 7.29 – 7.25 (m, 1H), 1.55 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 145.9, 143.2, 137.7, 134.6, 129.9, 128.4, 127.6, 126.7, 126.6, 126.1, 124.2, 118.4, 116.7, 113.9, 41.6, 28.7; MS (EI) *m/z* 436 (M^+, 100), 434 (M^+, 100).

8.2.3.13. 3-(2'-Chloro-5'-nitrophenyl)-7-methyl-N-pivaloylindole



31

The reaction was performed following the general procedure with $Pd(MeCN)_2Cl_2$ (8.4 mg, 0.03 mmol), **9-g** (0.035 g, 0.16 mmol), 2-chloro-5-nitrobenzoic acid (0.066 g, 0.32 mmol), Ag_2CO_3 (0.135 g, 0.49 mmol), DMSO (0.028 mL, 0.39 mmol) and DMF (1.6 mL). The crude product was purified by column chromatography (hexanes:EtOAc 98:2) to afford **31** as a yellow solid (0.033 g, 55%). m.p. 130–132 ºC; R_f 0.24 (hexanes:EtOAc 98:2); IR: 1709, 1519, 1338; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, 1H, *J* = 2.8 Hz), 8.18 (dd, 1H, *J* = 8.8, 2.8 Hz), 7.81 (s, 1H), 7.72 (d, 1H, *J* = 8.8 Hz), 7.37 (d, 1H, *J* = 7.6 Hz), 7.28 – 7.26 (m, 1H), 7.23 – 7.21 (m, 1H), 2.39 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 146.6, 140.4, 136.1, 134.1, 131.2, 128.9, 127.9, 126.5, 125.9, 125.8, 123.9, 123.0, 117.2, 116.5, 42.3, 29.2, 21.4; MS (EI) *m/z* 370 (M^+, 100).

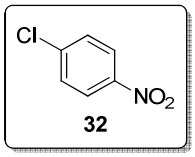
8.3. Experimental Chapter 3

8.3.1. General procedure for the Ag(I)-catalysed protodecarboxylation of *ortho* benzoic acids

A mixture of benzoic acid (0.5 mmol) and Ag_2CO_3 (0.05 mmol) in dry DMSO (2.5 mL) was stirred at 120 ºC for 16 hours. After this time the reaction was partitioned with Et_2O (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The two layers were separated and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL). The ethereal layer was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The product was obtained without further purification.

The benzene derivatives obtained are all known compounds, which are commercially available or previously described.

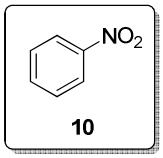
8.3.1.1. 1-Chloro-4-nitrobenzene



32

The reaction was carried out following the general procedure with 2-chloro-5-nitrobenzoic acid (0.102 g, 0.5 mmol) to afford **32** as a yellow solid (0.071 g, 90%). CAS: 100-00-5.

8.3.1.2. Nitrobenzene

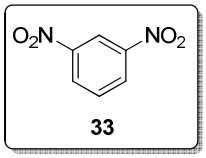


10

The reaction was carried out following the general procedure with 2-nitrobenzoic acid (0.084 g, 0.5 mmol) to afford **10** as a yellow oil (0.057 g, 91%). CAS: 98-95-3.

The same reaction was scaled up following the general procedure with 2-nitrobenzoic acid (4.2 g, 25 mmol) to afford **10** as a yellow oil (2.8 g, 91%). CAS: 98-95-3.

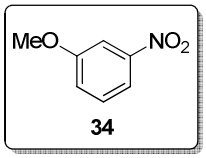
8.3.1.3. 1,3-Dinitrobenzene



33

The reaction was carried out following the general procedure with 2,4-dinitrobenzoic acid (0.111 g, 0.5 mmol) to afford **33** as a yellow solid (0.079 g, 94%). CAS: 99-65-0.

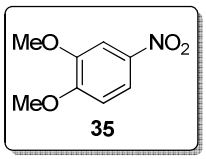
8.3.1.4. 1-Methoxy-3-nitrobenzene



34

The reaction was carried out following the general procedure with 4-methoxy-2-nitrobenzoic acid (0.100 g, 0.5 mmol) to afford **34** as a yellow solid (0.074 g, 96%). CAS: 555-03-3.

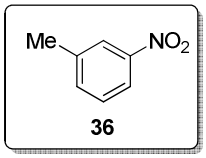
8.3.1.5. 1,2-Dimethoxy-4-nitrobenzene



35

The reaction was carried out following the general procedure with 4,5-methoxy-2-nitrobenzoic acid (0.116 g, 0.5 mmol) to afford **35** as a yellow solid (0.092 g, 100%). CAS: 709-09-1.

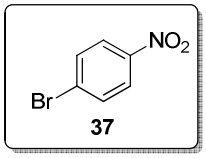
8.3.1.6. 3-Nitrotoluene



36

The reaction was carried out following the general procedure with 2-methyl-6-nitrobenzoic acid (0.093 g, 0.5 mmol) to afford **36** as a yellow liquid (0.059 g, 86%). CAS: 99-08-1.

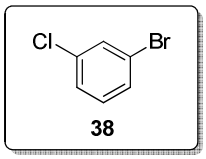
8.3.1.7 1-Bromo-4-nitrobenzene



37

The reaction was carried out following the general procedure using 2-bromo-5-nitrobenzoic acid (0.125 g, 0.5 mmol) to afford **37** as a white solid (0.098 g, 97%). CAS: 586-78-7.

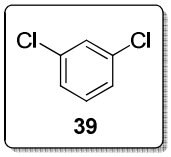
8.3.1.8. 1-Bromo-3-chlorobenzene



38

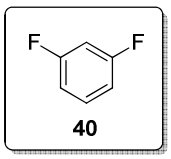
The reaction was carried out following the general procedure in a sealed vessel with 4-bromo-2-chlorobenzoic acid (0.024 g, 0.1 mmol)) and d_6-DMSO (0.5 mL) to afford **38** (99%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 108-37-2.

8.3.1.9. 1,3-Dichlorobenzene



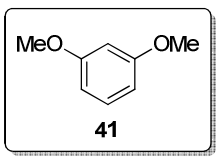
The reaction was carried out following the general procedure in a sealed vessel with 2,6-dichlorobenzoic acid (0.020 g, 0.1 mmol) and d_6-DMSO (0.5 mL) to afford **39** (96%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 541-73-1.

8.3.1.10. 1,3-Difluorobenzene



The reaction was carried out following the general procedure in a sealed vessel with 2,6-difluorobenzoic acid (0.016 g, 0.1 mmol) and d_6-DMSO (0.5 mL) to afford **40** (99%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 372-18-9.

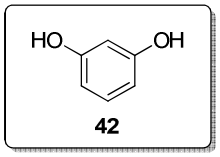
8.3.1.11. 1,3-Dimethoxybenzene



From 2,6-dimethoxybenzoic acid: the reaction was carried out following the general procedure with 2,6-dimethoxybenzoic acid (0.092 g, 0.5 mmol) to afford **41** as a colorless oil (0.063 g, 91%). CAS: 151-10-0.

From 2,4-dimethoxybenzoic acid: the reaction was carried out following the general procedure with 2,4-dimethoxybenzoic acid (0.092, 0.5 mmol) at 140 ºC to afford **41** as a colorless oil (0.066 g, 96%). CAS: 151-10-0.

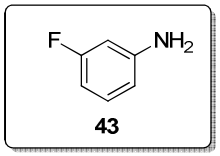
8.3.1.12. 1,3-Dihydroxybenzene



42

The reaction was carried out following the general procedure with 2,6-dihydroxybenzoic acid (0.077 g, 0.5 mmol) to afford **42** as a white solid (0.041 g, 71%). CAS: 108-46-3.

8.3.1.13. 3-Fluoroaniline



43

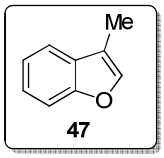
The reaction was carried out following the general procedure in a sealed vessel with 2-amino-6-fluorobenzoic acid (0.016 g, 0.1 mmol) and d_6-DMSO (0.5 mL) to afford **43** (95%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 372-19-0.

8.3.2. General procedure for protodecarboxylation of heteroaromatic carboxylic acids

A mixture carboxylic acid (0.5 mmol, 1.0 equiv.), Ag_2CO_3 (0.05 mmol, 0.1 equiv.), AcOH (0.025 mmol, 0.05 equiv.) in DMSO (1.0 mL) was stirred at 120 ºC. After 16 hours, the reaction was cooled down to room temperature and quenched with 2 M HCl (2 mL) and the aqueous phase extracted with EtOAc (5 × 5 mL). The combined organic layers were washed with brine (2 × 25 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave analytically pure product without further purification.

The following protodecarboxylated products were commercially available (CAS numbers given) or previously described. Their analytical data are identical with those reported in the literature.

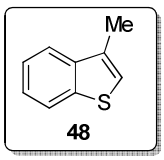
8.3.2.1. 3-Methylbenzofuran



47

The reaction was carried out following the general procedure with 3-methylbenzofuran-2-carboxylic acid (88.0 mg, 0.5 mmol). The reaction was quenched with 2 M HCl (2 mL) and the aqueous phase extracted with CH_2Cl_2 (5 × 5 mL) instead of EtOAc. This gave **47** as a liquid (58.2 mg, 88%). CAS: 21535-97-7.

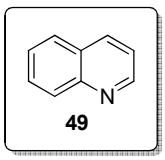
8.3.2.2. 3-Methylbenzothiophene



48

The reaction was carried out following the general procedure with 3-methylbenzothiophene-2-carboxylic acid (96.0 mg, 0.5 mmol) to give **48** as a liquid (74.0 mg, 100%). CAS: 1455-18-1.

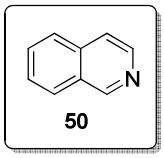
8.3.2.3. Quinoline



49

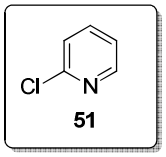
The reaction was carried out following the general procedure with quinoline-2-carboxylic acid (86.5 mg, 0.5 mmol) at 140 °C to give **49** as a liquid (58.2 mg, 90%). CAS: 91-22-5.

8.3.2.4. Isoquinoline



The reaction was carried out following the general procedure with isoquinoline-1-carboxylic acid (86.5 mg, 0.5 mmol) to give **50** as a liquid (59.4 mg, 92%). CAS: 119-65-3.

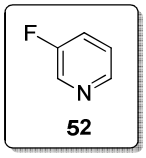
8.3.2.5. 2-Chloropyridine



From 6-chloropyridine-2-carboxylic acid: the reaction was carried out following the general procedure with 2-chloronicotinic acid (78.5 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) at 140 °C to give **51** (91%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 109-09-1.

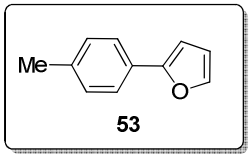
From 2-chloro-pyridine-3-carboxylic acid: the reaction was carried out following the general procedure with 6-chloronicotinic acid (78.5 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) at 140 °C to give **51** (97%) calculated by ^{1}H NMR using mesitylene as the internal standard.

8.3.2.6. 3-Fluoropyridine



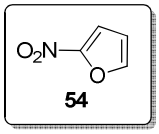
The reaction was carried out following the general procedure with 3-fluoroisonicotinic acid (70.5 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) to give **52** (100%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 372-47-4.

8.3.2.7. 2-p-Tolylfuran



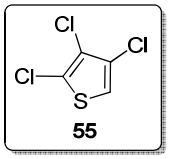
The reaction was carried out following the general procedure with 5-*p*-tolylfuran-2-carboxylic acid (101.0 mg, 0.5 mmol) without AcOH to give **53** as a yellow oil (73.5 mg, 93%). CAS: 17113-32-5.

8.3.2.8. 2-Nitrofuran



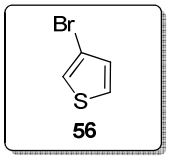
The reaction was carried following the general procedure with 5-nitrofuran-2-carboxylic acid (1.57 mg, 10.0 mmol, 1.0 equiv) to give **54** as a solid (995 mg, 88%). CAS: 609-39-2.

8.3.2.9. 2,3,4-Trichlorothiophene



The reaction was carried out following the general procedure with 3,4,5-trichlorothiophene-2-carboxylic acid (115 mg, 0.5 mmol) to give **55** as an oil (84.5 mg, 91%). CAS: 17249-78-4.

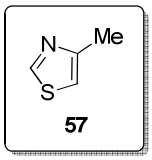
8.3.2.10. 3-Bromothiophene



56

The reaction was carried out following the general procedure with 3-bromothiophene-2-carboxylic acid (103 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) to give **56** (100%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 872-31-1.

8.3.2.11. 4-Methylthiazole



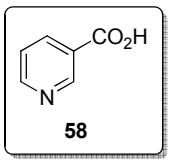
57

The reaction was carried out following the general procedure with 4-methylthiazole-5-carboxylic acid (71.5 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) to give **57** (100%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 693-95-8.

8.3.3. General procedure for the regioselective protodecarboxylation of (hetero)aromatic dicarboxylic acids

A mixture carboxylic acid (0.5 mmol, 1.0 equiv.), Ag_2CO_3 (0.05 mmol, 0.1 equiv.), AcOH (0.025 mmol, 0.05 equiv.) in DMSO (1.0 mL) was stirred at 120 ºC. After 16 hours, the reaction was cooled down to room temperature and quenched with 2 M HCl (2 mL) and the aqueous phase extracted with EtOAc (5 × 5 mL). The combined organic layers were washed with brine (2 × 25 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave analytically pure product without further purification.

8.3.3.1. Nicotinic acid

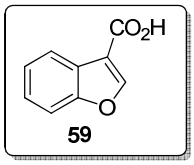


58

From pyridine-2,5-dicarboxylic acid: the reaction was carried out following the general procedure with pyridine-2,5-dicarboxylic acid (83.5 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) at 140 °C to give **58** (100%) calculated by ^{1}H NMR using mesitylene as the internal standard. CAS: 59-67-6.

From pyridine-2,3-dicarboxylic acid: the reaction was carried out following the general procedure with pyridine-2,3-dicarboxylic acid (83.5 mg, 0.5 mmol) in d_6-DMSO (1.0 mL) to give **58** (100%) calculated by ^{1}H NMR using mesitylene as the internal standard.

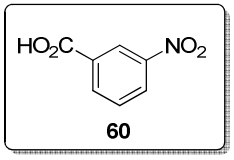
8.3.3.2. Benzofuran-3-carboxylic acid



59

The reaction was carried out following the general procedure with benzofuran-2,3-dicarboxylic acid (103 mg, 0.5 mmol) at 140 °C to give **59** as a solid (68.9 mg, 85%). CAS: 26537-68-8.

8.3.3.3 3-Nitrobenzoic acid

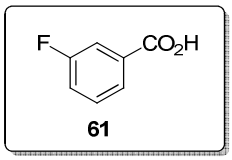


60

From 2-nitroterephthalic acid: the reaction was carried out following the general procedure with 2-nitroterephthalic acid (105.5 mg, 0.5 mmol) to give **60** as a solid (77.7 mg, 93%). CAS: 121-92-6.

From 3-nitrophthalic acid: the reaction was carried out following the general procedure with 3- nitrophthalic acid (105.5 mg, 0.5 mmol) to give **60** as a solid (76.8 mg, 92%).

8.3.3.4. 3-Fluorobenzoic acid



61

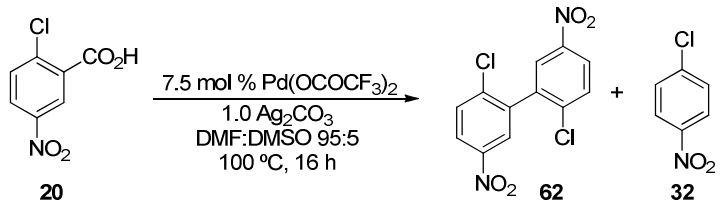
The reaction was carried out following the general procedure with 3-fluorophthalic acid (92.0 mg, 0.5 mmol) to give **61** as a solid (60.0 mg, 86%). CAS: 455-38-9.

8.4. Experimental Chapter 4

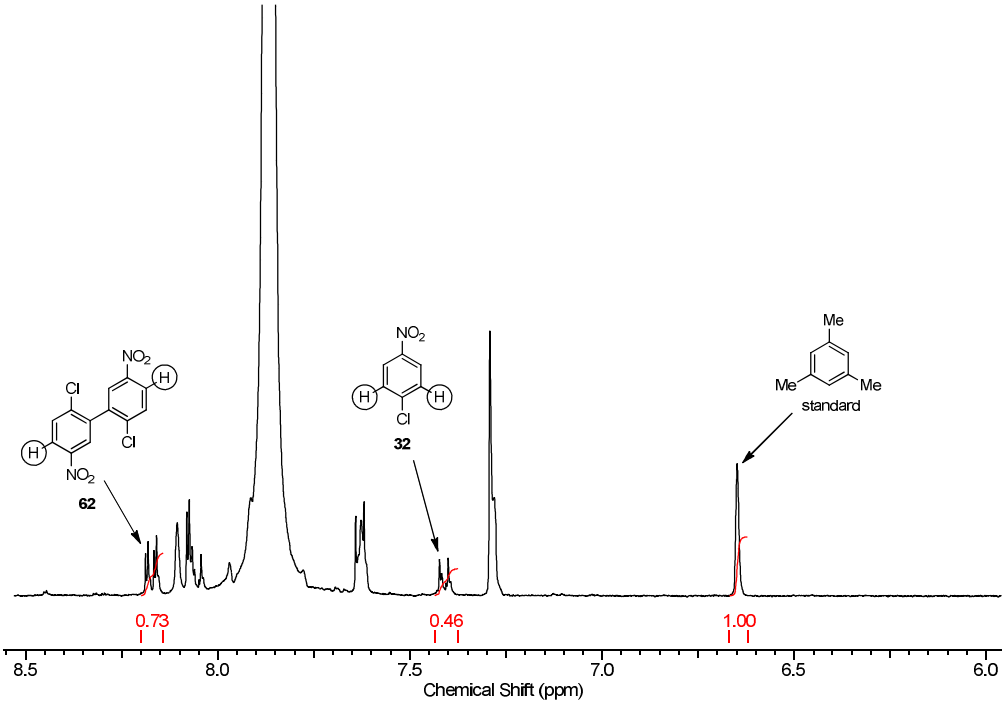
8.4.1. Optimisation of the decarboxylative homocoupling of (hetero)aromatic carbobylic acids

A mixture of $Pd(TFA)_2$ (8.3 mg, 0.025 mmol), 2-chloro-5-nitrobenzoic acid (**20**) and Ag_2CO_3 (69 mg, 0.25 mmol) in 1.25 mL of DMF: DMSO (95:5) at 110 ºC for 16 h in a sealed vessel. After this time, the solution was filtered through a plug of SiO_2 and flushed with EtOAc. The solvent was evaporated to dryness and mesitylene (1 mL of 0.082 M in $CDCl_3$, 0.082 mmol) was added. The crude was then analysed by ^1H NMR and GCMS.

A ^1H NMR for the crude of the reaction described in Table 19, entry 1 is shown below.



20 **62** **32**



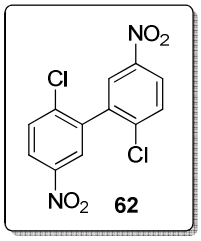
In this case, the reaction afforded 73% of dimer **62** and 23% of **32**.

8.4.2. General procedure for the synthesis of dimers

A suspension of aromatic carboxylic acid (0.5 mmol), Ag_2CO_3 (0.138 g, 0.5 mmol) and $Pd(TFA)_2$ (0.012 g, 0.036 mmol) in 10 mL of DMF:DMSO 95:5 (0.05 M) was stirred at 120 ºC for 16 h in a sealed vessel. After this time, the reaction mixture was cooled down to room temperature and filtered through a plug of silica gel with EtOAc. The fitrate was washed with a saturated solution of $NaHCO_3$ (5 × 20 mL), brine (5 × 20 mL) and the organic layer was evaporated to dryness under reduced pressure. The crude was purified by column chromatography to afford the desired product.

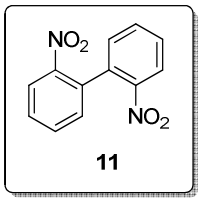
Analytical data for products **11**, and **63** matched with the previously reported in the literature.

8.4.2.1. 2,2'-Dichloro-5,5'-dinitrobiphenyl



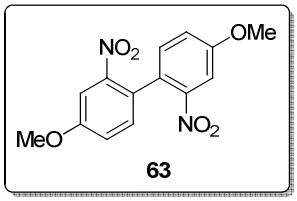
The reaction was carried out following the general procedure with 2-chloro-5-nitrobenzoic acid (0.101 g, 0.5 mmol) in 5 mL of DMF:DMSO (95:5). The crude product was purified by column chromatography (hexanes:EtOAc 9:1) to afford **62** as a white solid (0.078 g, 68%). m.p. 193–194 ºC; R_f 0.31 (hexanes:CH_2Cl_2:EtOAc 85:14:1); IR: 1565, 1344; ^{1}H NMR (400 MHz) δ 8.31 (dd, 2H, *J* = 8.8, 2.7 Hz), 8.22 (d, 2H, *J* = 2.7 Hz), 7.74 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (101 MHz) δ 146.5, 140.6, 137.4, 130.9, 126.1, 125.1; HRMS(EI) calcd. $C_{12}H_6Cl_2N_2O_4$: (M^+), 311.9705, found: (M^+), 311.9693.

8.4.2.2. 2,2'-Dinitrobiphenyl[103]



The reaction was carried out following the general procedure with 2-nitrobenzoic acid (0.084 g, 0.5 mmol) at 115 ºC. The crude product was purified by column chromatography (hexanes:EtOAc 9:1) to afford **11** as a yellow solid (0.057 g, 94%) R_f 0.23 (hexanes:EtOAc 9:1); ^{1}H NMR (400 MHz) δ 8.23 (d, 2H, *J* = 8.4 Hz), 7.72 – 7.68 (m, 2H), 7.63 – 7.59 (m, 2H), 7.31 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (101 MHz) δ 147.2, 134.2, 133.4, 130.9, 129.1, 124.9.

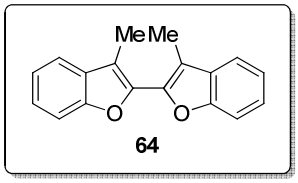
8.4.2.3. 4,4'-Dimethoxy-2,2'-dinitrobiphenyl[104]



63

The reaction was carried out following the general procedure with 4-methoxy-2-nitrobenzoic acid (0.099 g, 0.5 mmol) at 115 ºC. The crude product was purified by column chromatography (hexanes:EtOAc 9:1) to afford **63** as a yellow solid (0.058 g, 76%%); R_f 0.42 (hexanes:EtOAc 9:1); ^{1}H NMR (400 MHz) δ 7.68 (s, 2H), 7.19 (m, 4H), 3.93 (s, 6H); ^{13}C NMR (101 MHz) δ 159.6, 148.2, 132.2, 125.7, 119.7, 109.5, 56.0.

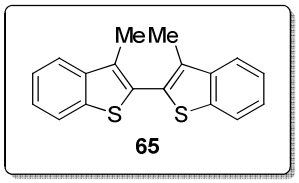
8.4.2.4. 3,3'-Dimethyl-2,2'-bibenzo[b]furan



64

The reaction was carried out following the general procedure with 3-methylbenzofuran-2-carboxylic acid (0.088 g, 0.5 mmol) at 115 ºC. The crude product was purified by column chromatography (hexanes) to afford **64** (0.051 g, 78%); m.p. 119–121 ºC; R_f 0.35; IR: 1475, 1329, 1221, 1112, 736; ^{1}H NMR (400 MHz) δ 7.54 (d, 2H, J = 8.0 Hz), 7.47 (d, 2H, J = 7.9 Hz), 7.32 – 7.22 (m, 4H), 2.56 (s, 6H); ^{13}C NMR (101 MHz) δ 154.5, 144.0, 130.2, 124.8, 122.7, 119.5, 114.3, 111.0, 8.9; HRMS (ESI) calcd. $C_{18}H_{15}O_2$: $(M+H)^+$, 263.1067; found: $(M+H)^+$, 263.1067.

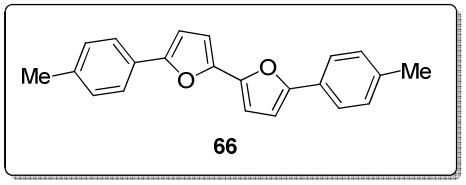
8.4.2.5. 3,3'-Dimethyl-2,2'-bibenzo[b]thiophene



65

The reaction was carried out following the general procedure with 3-methylbenzothiophene-2-carboxylic acid (0.096, 0.5 mmol) at 130 ºC. The crude product was purified by column chromatography (hexanes) to afford **65** (0.047, 64%) m.p. 124–126 ºC; R_f 0.33 (hexanes); IR: 1429, 912, 761, 752; ^{1}H NMR (400 MHz) δ 7.87 (d, 2H, *J* = 8.8 Hz), 7.79 (d, 2H, *J* = 8.2 Hz), 7.49 – 7.40 (m, 4H), 2.42 (s, 6H); ^{13}C NMR (101 MHz) δ 140.4, 140.1, 131.6, 129.9, 124.8, 124.3, 122.3, 122.1, 12.9; HRMS (ESI) calcd. $C_{18}H_{15}S_2$: $(M+H)^+$, 295.0610; found: $(M+H)^+$, 295.0608.

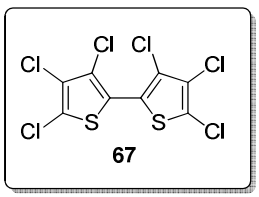
8.4.2.6. 5,5'-Bis-p-tolyl-2,2'-bifuran



66

The reaction was carried out following the general procedure with 5-*p*-tolylfuran-2-carboxylic acid (0.101 g, 0.5 mmol), $Pd(TFA)_2$ (0.024 g, 0.072 mmol) in 20 mL of DMF:DSMO (95:5) at 125 ºC. The crude product was purified by column chromatography (hexanes) to afford **66** (0.044 g, 56%); m.p. 176–179 ºC; R_f 0.29 (hexanes) IR: 1505, 1016, 819, 783; ^{1}H NMR (400 MHz) δ 7.63 (d, 4H, *J* = 8.0 Hz), 7.22 (d, 4H, *J* = 8.0 Hz), 6.71 – 6.69 (m, 4H), 2.39 (s, 6H); ^{13}C NMR (101 MHz) δ 153.4, 145.7, 137.3, 129.4, 127.9, 123.7, 107.2, 106.3; HRMS (ESI) calcd. $C_{22}H_{20}O_2$: $(M+H)^+$, 315.1380; found: $(M+H)^+$, 315.1376.

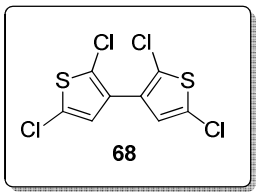
8.4.2.7. Perchloro-2,2'-bithiophene



67

The reaction was carried out following the general procedure with 3,4,5-trichlorothiophene-2-carboxylic acid (0.115 g, 0.5 mmol). The crude product was purified by column chromatography (hexanes) to afford **67** (0.061 g, 66%); m.p. 182–184 ºC; R_f 0.8 (hexanes); IR: 1493, 1406, 1315, 1279, 939, 778; ^{13}C NMR (101 MHz, $CDCl_3$ + d_6-DMSO) δ 126.6, 123.9, 123.8, 123.2; HRMS (ESI) calcd. $C_8HCl_6S_2$: $(M+H)^+$, 370.7645; found: $(M+H)^+$, 370.7644.

8.4.2.8. 2,2',5,5'-Tetrachloro-3,3'-bithiophene

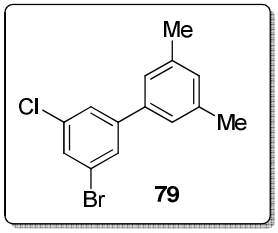


68

The reaction was carried out following the general procedure with 2,5-dichlorothiophene-2-carboxylic acid (0.099 g, 0.5 mmol) in 20 mL of DMF:DMSO (95:5). The crude product was purified by column chromatography (hexanes) to afford **68** (0.043 g, 57%); m.p. 106–108 ºC, R_f 0.84 (hexanes); IR: 1518, 1404, 1057, 1008, 818; ^{1}H NMR (400 MHz) δ 6.94 (s, 2H); ^{13}C NMR (101 MHz) δ 130.6, 127.4, 127.0, 125.1; HRMS (ESI) calcd. $C_8H_3Cl_3S_2$: $(M+H)^+$, 302.8425; found: $(M+H)^+$, 302.8428.

8.5. Experimental Chapter 5.

8.5.1. 3-Bromo-5-chloro-3',5'-dimethyl-1,1'-biphenyl

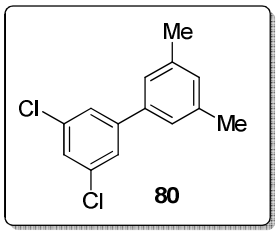


79

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 4-bromo-2-chlorobenzoic acid (122 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 µL, 0.75 mmol) in acetic acid (100 µL) was heated at 130 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The

filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3-bromo-5-chloro-3',5'-dimethyl-1,1'-biphenyl (**79**) as a white solid (105 mg, 71%). m.p. 94–96°C; R_f 0.60 (hexanes); IR: 1554, 834, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.49–7.46 (m, 2H), 7.15 (s, 2H), 7.05 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 138.6, 138.4, 135.3, 130.1, 129.7, 128.5, 126.1, 125.0, 122.9, 21.4; HRMS (EI) calcd. $C_{14}H_{12}BrCl$: (M^+), 293.9811; found: (M^+), 293.9810.

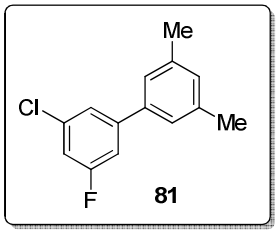
8.5.2. 3,5-Dichloro-3',5'-dimethyl-1,1'-biphenyl



80

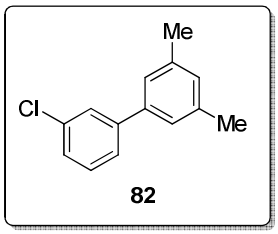
A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2,4-dichlorobenzoic acid (96 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 µL, 0.75 mmol) in acetic acid (100 µL) was heated at 130 ºC for 16 h. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3,5-dichloro-3',5'-dimethyl-1,1'-biphenyl (**80**) as a white solid (98 mg, 78%). mp: 102–104 ºC; R_f 0.65 (hexanes); IR: 1592, 1556, 1366, 833, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, 2H, J = 1.6 Hz), 7.32 (t, 1H, J = 1.6 Hz), 7.16 (s, 2H), 7.05 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) 144.4, 138.7, 138.5, 135.1, 130.1, 126.9, 125.6, 124.9, 21.3; HRMS (CI) calcd. $C_{14}H_{13}Cl_2$: ($[M+H]^+$), 251.0389; found: ($[M+H]^+$), 251.0392.

8.5.3. 3-Chloro-5-fluoro-3',5'-dimethyl-1,1'-biphenyl



A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2-chloro-4-fluorobenzoic acid (87 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3-chloro-5-fluoro-3',5'-dimethyl-1,1'-biphenyl (**81**) as a white solid (97 mg, 83%). mp: 68–70 ºC; R_f 0.62 (hexanes); IR: 1606, 1573, 1399, 1240, 1167, 1078, 946, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.37 (m, 1H), 7.21–7.17 (m, 3H), 7.08–7.04 (m, 2H), 2.4 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (d, J = 249.7 Hz), 144.2 (d, J = 8.1 Hz), 138.0 (d, J = 2.0 Hz), 137.9, 134.5 (d, J = 11.1 Hz), 129.4, 124.3, 122.5 (d, J = 3.0 Hz), 113.9 (d, J = 25.0 Hz), 111.9 (J = 22.2 Hz), 20.7; HRMS (CI) calcd. $C_{14}H_{13}ClF$: ($[M+H]^+$), 235.0684; found: ($[M+H]^+$), 235.0684.

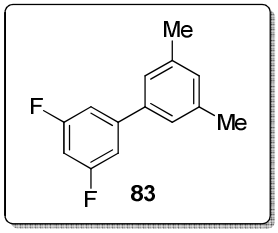
8.5.4. 3-Chloro-3',5'-dimethyl-1,1'-biphenyl



A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2-chlorobenzoic acid (78 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were

combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3-chloro-3',5'-dimethyl-1,1'-biphenyl (**82**) as a colorless oil (69 mg, 64%). R_f 0.45 (hexanes). IR: 1592, 1568, 1100, 846, 782, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (td, 1H, *J* = 1.6, 0.8 Hz), 7.47 (dt, 1H, *J* = 7.4, 1.6 Hz), 7.36 (td, 1H, *J* = 7.7, 0.4 Hz), 7.32 (ddd, 1H, *J* = 7.9, 2.0, 1.4 Hz), 7.21 (s, 2H), 7.05 (s, 1H), 2.40 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 139.8, 138.4, 134.5, 129.8, 129.5, 127.3, 127.1, 125.3, 125.0, 21.4; HRMS (EI) calcd. $C_{14}H_{13}Cl$: (M^+), 216.0701; found: (M^+), 216.0702.

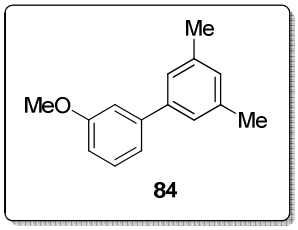
8.5.5. 3,5-Difluoro-3',5'-dimethyl-1,1'-biphenyl



83

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2,4-difluorobenzoic acid (79 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3,5-difluoro-3',5'-dimethyl-1,1'-biphenyl (**83**) as a colorless oil (93 mg, 85%). R_f 0.58 (hexanes). IR: 1623, 1591, 1266, 1110, 988, 843; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.17 (m, 2H), 7.13–7.08 (m, 2H), 7.06–7.05 (m, 1H), 6.78 (tt, 1H, *J* = 8.8, 2.4 Hz), 2.4 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (dd, *J* = 248.4, 13.1 Hz), 144.9 (t, *J* = 9.1 Hz), 138.9 (t, *J* = 2.0 Hz), 138.6, 130.0, 125.1, 109.9 (dd, *J* = 18.2, 7.1 Hz), 102.2 (t, *J* = 25.2 Hz), 21.0; HRMS (EI) calcd. $C_{14}H_{12}F_2$: (M^+), 219.0980; found: (M^+), 219.0980.

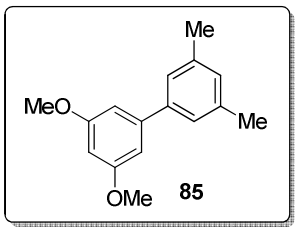
8.5.6. 3-Methoxy-3',5'-dimethyl-1,1'-biphenyl[105]



84

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2-methoxybenzoic acid (76 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes:EtOAc 99:1) to afford 3-methoxy-3',5'-dimethyl-1,1'-biphenyl (**84**) as a colorless oil (65 mg, 61%). R_f 0.27 (hexanes:EtOAc 99:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, 1H, J = 7.6 Hz), 7.21 (s, 2H), 7.17 (d, 1H, J = 7.6 Hz), 7.11 (s, 1H), 7.01 (s, 1H), 6.89 (d, 1H, J = 7.6 Hz), 3.88 (s, 3H), 2.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 142.0, 140.1, 137.2, 128.6, 128.0, 124.1, 118.7, 111.8, 111.6, 54.3, 20.4.

8.5.7. 3,5-Dimethoxy-3',5'-dimethyl-1,1'-biphenyl

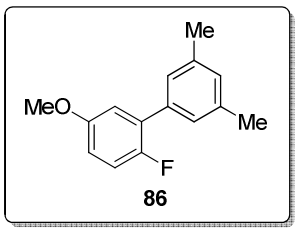


85

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2,4-dimethoxybenzoic acid (91 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to

dryness. The crude product was purified by *flash* column chromatography (hexanes:EtOAc 98:2) to afford 3,5-dimethoxy-3',5'-dimethyl-1,1'-biphenyl (**85**) as a colorless oil (73 mg, 60%). R_f 0.19 (hexanes:EtOAc 98:2). IR: 1592, 1201, 1152, 1047, 830; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 7.02 (s, 1H), 6.72 (d, 2H, J = 2.4 Hz), 6.46 (t, 1H, J = 2.4 Hz), 3.86 (s, 6H), 2.39–2.38 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 143.7, 141.2, 138.2, 129.2, 125.1, 105.4, 99.2, 55.4, 21.4. HRMS (CI) calcd. $C_{16}H_{19}O_2$: $[M+H]^+$, 243.1380; found: $[M+H]^+$, 243.1382.

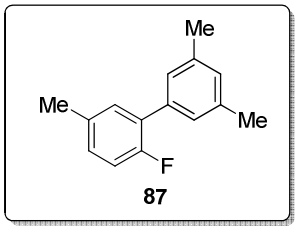
8.5.8. 6-Fluoro-3-methoxy-3',5'-dimethyl-1,1'-biphenyl



86

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 5-fluoro-2-methoxybenzoic acid (85 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes:EtOAc 98:2) to afford 6-fluoro-3-methoxy-3',5'-dimethyl-1,1'-biphenyl (**86**) as a colorless oil (90 mg, 78%). R_f 0.19 (hexanes:EtOAc 98:2). IR: 1600, 1499, 1467, 1205, 1036, 850, 737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 2H), 7.09–7.05 (m, 2H), 6.96–6.93 (m, 1H), 6.85–6.81 (m, 1H), 3.84 (s, 3H), 2.40 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 (d, J = 2.1 Hz), 154.2 (d, J = 240.8 Hz), 137.9, 135.7 (d, J = 1.3 Hz), 129.8 (d, J = 15.4 Hz), 129.4, 126.8 (d, J = 2.7 Hz), 116.5 (d, J = 25.0 Hz), 115.4 (d, J = 3.2 Hz), 113.7 (d, J = 8.1 Hz), 55.8, 21.4; HRMS (CI) calcd. $C_{15}H_{16}FO$: ($[M+H]^+$), 231.1180; found: ($[M+H]^+$), 231.1183.

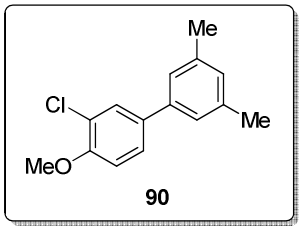
8.5.9. 3-Methyl-3',5'-dimethyl-1,1'-biphenyl



87

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2-toluic acid (69 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 µL, 0.75 mmol) in acetic acid (100 µL) was heated at 130 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3-methyl-3',5'-dimethyl-1,1'-biphenyl (**87**) as a colorless oil (55 mg, 56%). R_f 0.78 (hexanes); IR: 1603, 1463, 851, 778, 689; ^{1}H NMR (101 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.33 (t, 1H, *J* = 7.4 Hz), 7.23 (s, 2H), 7.16 (d, 1H, *J* = 7.4 Hz), 7.01 (s, 1H), 2.44 (s, 3H), 2.40 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5, 141.4, 138.2, 128.8, 128.5, 128.0, 127.8, 125.1, 124.3 (×2), 21.6, 21.4; HRMS (EI) calcd.: (M^+), 196.1248; found: (M^+), 196.1247.

8.5.10. 3-Chloro-4-methoxy-3',5'-dimethyl-1,1'-biphenyl

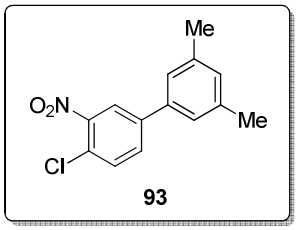


90

A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2-chloro-3-methoxybenzoic acid (93 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 µL, 0.75 mmol) in acetic acid (100 µL) was heated at 150 ºC for 16 h. After this time, Ag_2CO_3 (138 mg, 0.50 mmol) in dry DMSO (2.5 mL) was added and the reaction stirred for further 3 h at 170 ºC. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted

with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3-chloro-4-methoxy-3',5'-dimethyl-1,1'-biphenyl (**90**) as a yellow oil (72 mg, 58%). R_f 0.18 (hexanes). IR: 1600, 1503, 1455, 1253, 1063, 817, 693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 1H, *J* = 2.4 Hz), 7.44 (dd, 1H, *J* = 8.4, 2.4 Hz), 7.16 (s, 2H), 7.00–6.98 (m, 2H), 3.95 (s, 3H), 2.39 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 139.5, 138.4, 134.9, 128.9, 126.2, 124.6, 122.6, 112.2, 56.3, 21.4; HRMS (CI) calcd. $C_{15}H_{16}ClO$: ($[M+H]^+$), 247.0884; found: ($[M+H]^+$), 247.0885.

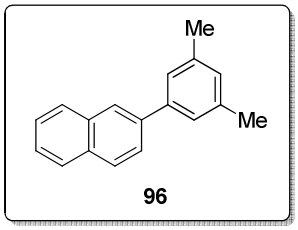
8.5.11. 4-Chloro-3-nitro-3',5'-dimethyl-1,1'-biphenyl



93

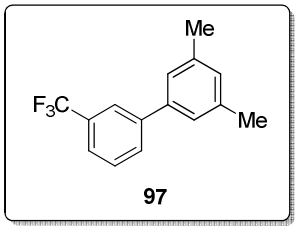
A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 3-chloro-2-nitrobenzoic acid (101 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (218 μL, 0.75 mmol) in acetic acid (100 μL) was heated at 130 ºC for 16 h. After this time, Ag_2CO_3 (138 mg, 0.50 mmol) in dry DMSO (2.5 mL) was added and the reaction stirred for further 3 h at 130 ºC. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 4-chloro-3-nitro-3',5'-dimethyl-1,1'-biphenyl (**93**) as a yellow solid (73 mg, 56%). mp: 108–110 ºC; R_f 0.16 (hexanes); IR: 1600, 1519, 1334, 1043, 821, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 2.0 Hz), 7.71 (dd, 1H, *J* = 8.4, 2.0 Hz), 7.58 (d, 1H, *J* = 8.4 Hz), 7.19 (s, 2H), 7.09 (s, 1H), 2.40 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 141.6, 138.9, 137.5, 132.0, 131.5, 130.4, 125.4, 124.8, 123.9, 21.3; HRMS (EI) calcd. $C_{14}H_{12}ClNO_2$: (M^+), 261.0551; found: (M^+), 261.0554.

8.5.12. 2-(3,5-Dimethylphenyl)naphthalene[106]



A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 1-napthoic acid (86 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (143 μL, 0.50 mmol) in acetic acid (100 μL) was heated at 150 ºC for 16 h. After this time, Ag_2CO_3 (138 mg, 0.50 mmol) in dry DMSO (2.5 mL) was added and the reaction stirred for further 4 h at 170 ºC. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 2-(3,5-dimethylphenyl)naphtalene (**96**) as a colorless solid (67 mg, 58%). R_f 0.28 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.94–7.87 (m, 3H), 7.76 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.54–7.48 (m, 2H), 7.37 (s, 2H), 7.06 (s, 1H), 2.45 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 138.8, 138.4, 133.7, 132.6, 129.0, 128.2, 128.1, 127.6, 126.2, 125.8, 125.76, 125.72, 125.4, 21.4.

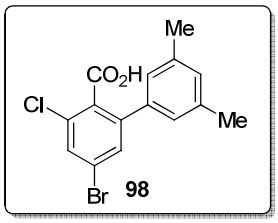
8.5.13. 3-Trifluoromethyl-3',5'-dimethyl-1,1'-biphenyl



A mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.50 mmol), 2-trifluoromethylbenzoic acid (95 mg, 0.50 mmol), 1-iodo-3,5-dimethylbenzene (143 μL, 0.50 mmol) in acetic acid (100 μL) was heated at 150 ºC for 16 h. After this time, Ag_2CO_3 (138 mg, 0.50 mmol) in dry DMSO (2.5 mL) was added and the reaction stirred for further 4 h at 170 ºC. The reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with 5% aqueous KOH and extracted

with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4 anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (hexanes) to afford 3-trifluoromethyl-3',5'-dimethyl-1,1'-biphenyl (**97**) as a colorless oil (75 mg, 60%). R_f 0.52 (hexanes). IR: 1600, 1338, 1124, 846, 797, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.76 (d, 1H, *J* = 7.6 Hz), 7.61–7.52 (m, 2H), 7.23 (s, 2H), 7.06 (s, 1H), 2.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 139.8, 138.6, 131.0 (q, *J* = 31.9 Hz), 130.4 (q, *J* = 1.3 Hz), 129.7, 129.1, 125.1, 124.2 (q, *J* = 273.4 Hz), 123.9 (q, *J* = 3.9 Hz), 123.7 (d, *J* = 3.7 Hz), 21.4; HRMS (CI) calcd. $C_{15}H_{14}F_3$: ($[M+H]^+$), 251.1042; found: ($[M+H]^+$), 251.1043.

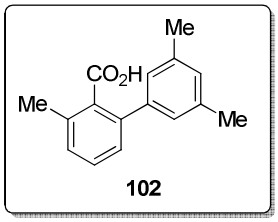
8.5.14. 5-Bromo-3-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid



98

A mixture of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), Ag_2CO_3 (276 mg, 1.00 mmol), 4-bromo-2-chlorobenzoic acid (236 mg, 1.00 mmol) and 1-iodo-3,5-dimethylbenzene (436 µL, 0.75 mmol) in acetic acid (200 µL) was heated at 120 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with HCl and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over $MgSO_4$ anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (CH_2Cl_2:EtOAc 9:1) to afford 5-bromo-3-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**98**) as a white solid (235 mg, 69%). mp 166–168 ºC; R_f 0.17 (CH_2Cl_2:EtOAc 9:1); IR: 2913, 1696, 1574, 1546, 1282, 843, 818, 703; ^{1}H NMR (101 MHz, $CDCl_3$) δ 7.59 (d, 1H, *J* = 2.0 Hz), 7.46 (d, 1H, *J* = 2.0 Hz), 7.04 (s, 1H), 7.01 (s, 2H), 2.33 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 143.4, 138.3, 137.7, 131.9, 131.4, 130.8, 130.7, 130.4, 126.0, 123.8, 21.2.

8.5.15. 3,3',5-trimethyl-[1,1'-biphenyl]-2-carboxylic acid[107]



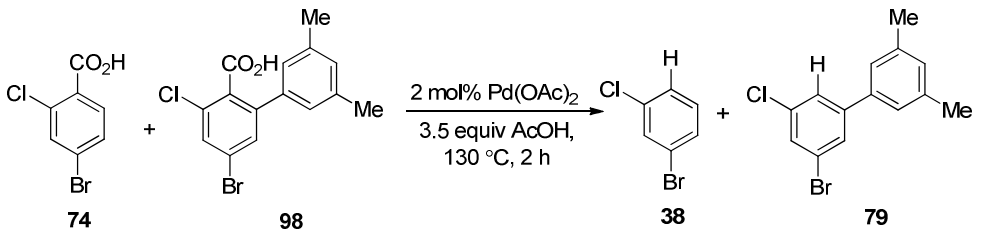
102

A mixture of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), Ag_2CO_3 (276 mg, 1.00 mmol), *o*-toluic acid (136 mg, 1.00 mmol) and 1-iodo-3,5-dimethylbenzene (436 µL, 0.75 mmol) in acetic acid (200 µL) was heated at 120 ºC for 16 h. After this time, the reaction mixture was filtered through a plug of celite with CH_2Cl_2. The filtrate was washed with HCl and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over $MgSO_4$ anhydrous, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (CH_2Cl_2:EtOAc 9:1) to afford 3,3',5-trimethyl-[1,1'-biphenyl]-2-carboxylic acid (**98**) as a white solid (169 mg, 70%). R_f 0.21 (CH_2Cl_2:EtOAc 9:1); ^{1}H NMR (101 MHz, $CDCl_3$) δ 7.37 (t, 1H, J = 7.8 Hz), 7.23 (d, 2H, J = 7.8 Hz), 7.07 (s, 2H), 7.01 (s, 1H), 2.47 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 140.5, 140.3, 137.9, 135.3, 132.0, 129.6, 129.2, 129.0, 127.4, 126.2, 21.3, 19.9.

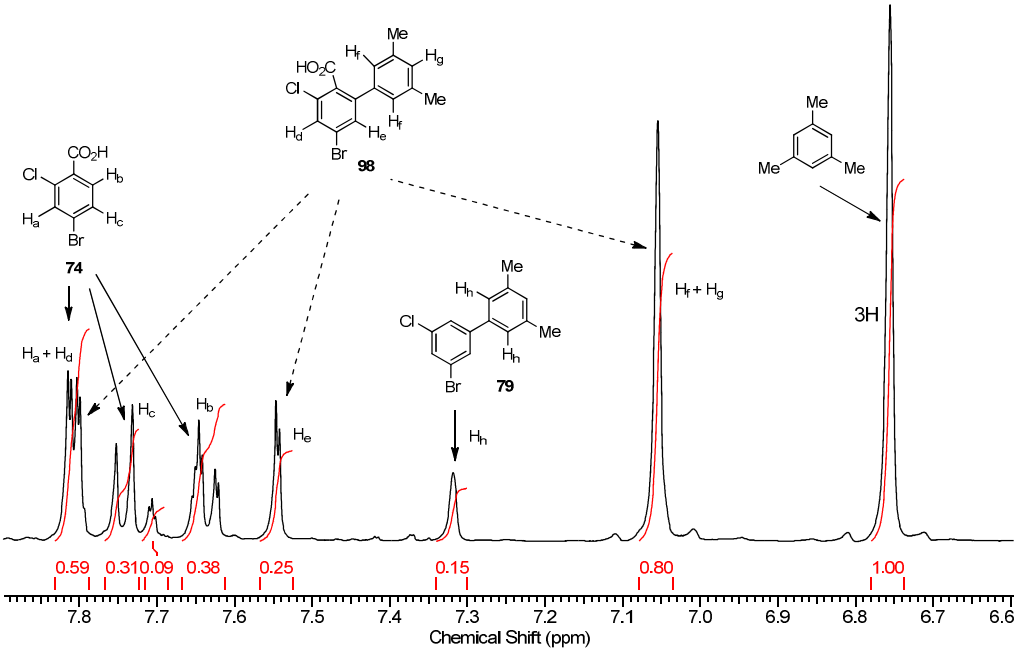
8.5.16. Competition experiments between 74 and 98

The ^{1}H NMR shown below corresponds to the reaction described in Table 23, entry 3.

A mixture of 4-bromo-2-chlorobenzoic acid (14.7 mg, 0.0625 mmol), benzoic acid **98** (21.2 mg, 0.0625 mmol) and $Pd(OAc)_2$ (0.3 mg, 0.00125 mmol) in 50 µL of AcOH were heated at 130 ºC for 2 h. After this time, mesitylene and d_6-DMSO were added to the mixture and a ^{1}H NMR was carried out.



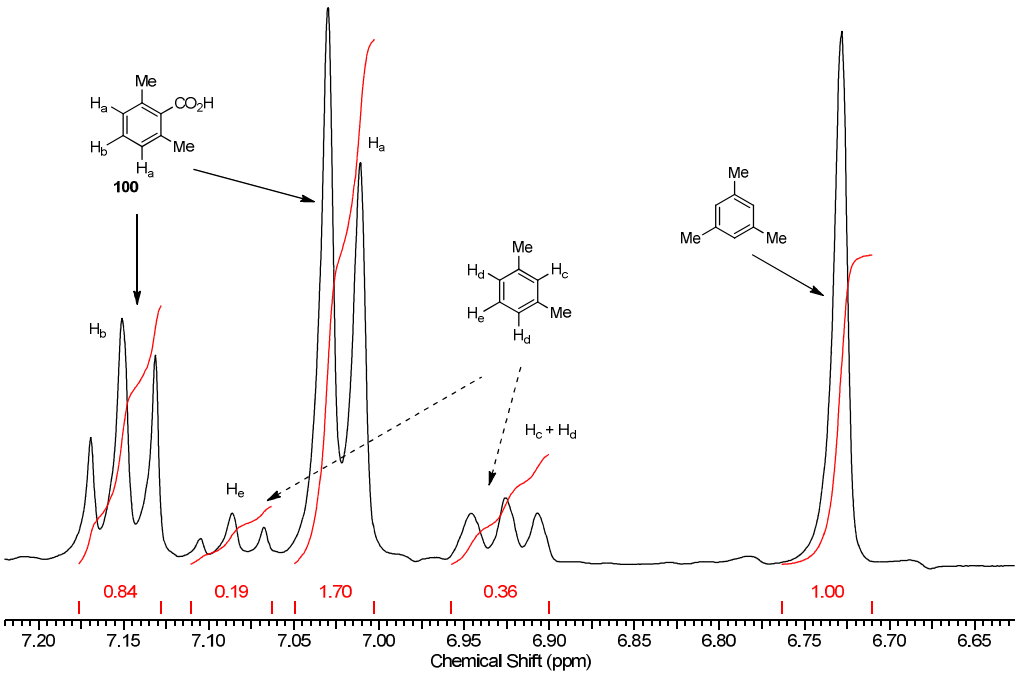
74 **98** **38** **79**



The rest of the reactions were carried out using the same protocol but changing the reaction conditions as described in Table 23.

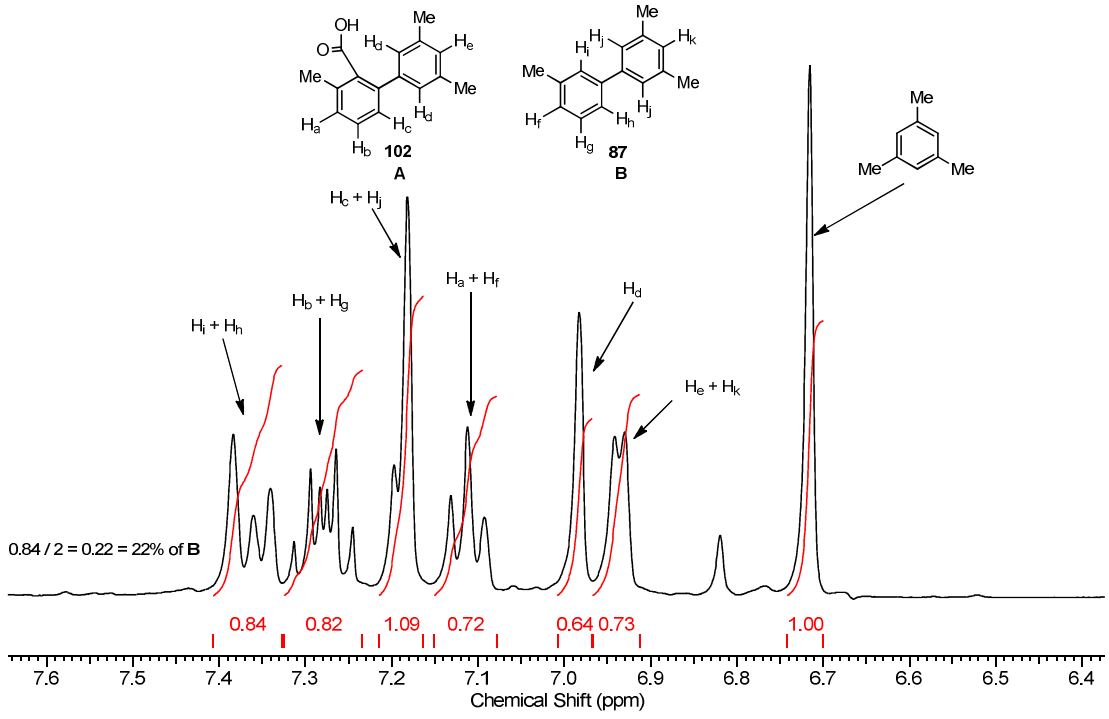
8.5.17. Decarboxylation experiments of hindered substrates

Table 24, entry 1: A mixture of 2,6-dimethoxybenzoic acid (37.5 mg, 0.25 mmol) and $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) in 0.2 mL of AcOH (14 equiv) at 130 ºC for 2 h. After this time, mesitylene and d_6-DMSO were added to the mixture and a ^1H NMR was carried out.

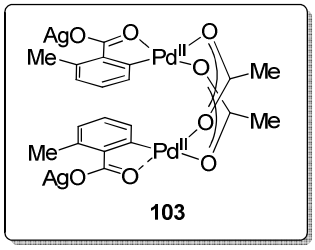


The rest of the reactions were carried out using the same protocol but changing the the benzoic acid as described in Table 24.

Table 24, entry 7: A mixture of benzoic acid **102** (60.0 mg, 0.25 mmol) and $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) in 0.2 mL of AcOH (14 equiv) at 130 ºC for 16 h. After this time, mesitylene and d_6-DMSO were added to the mixture and a ^1H NMR was carried out.



8.5.18. Formation of palladacycle 103



103

A mixture of *o*-toluic acid (34 mg, 0.25 mmol), Ag_2CO_3 (35 mg, 0.125 mmol) and $Pd(OAc)_2$ (56 mg, 0.25 mmol) in AcOH (0.1 mL) was heated at 100 ºC for 3.5 h. After this, time, the mixture was filtered through a sinter funnel and the black solid was washed with cold Et_2O (10 mL) and cold CH_2Cl_2 (10 mL). The solid was collected and dried under vacuum for 16 h in the absence of light affording 49 mg (48%) of palladacycle **103**. IR: 1536, 1395, 1272; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.47 (d, 2H, *J* = 7.5 Hz), 6.91 (t, 2H, *J* = 7.4 Hz), 6.84 (d, 2H, *J* = 7.4 Hz), 2.43 (s, 6H), 1.80 (s, 6H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 180.1, 177.0, 139.9, 139.0, 138.3, 128.6, 128.4, 128.2, 23.8, 18.8.

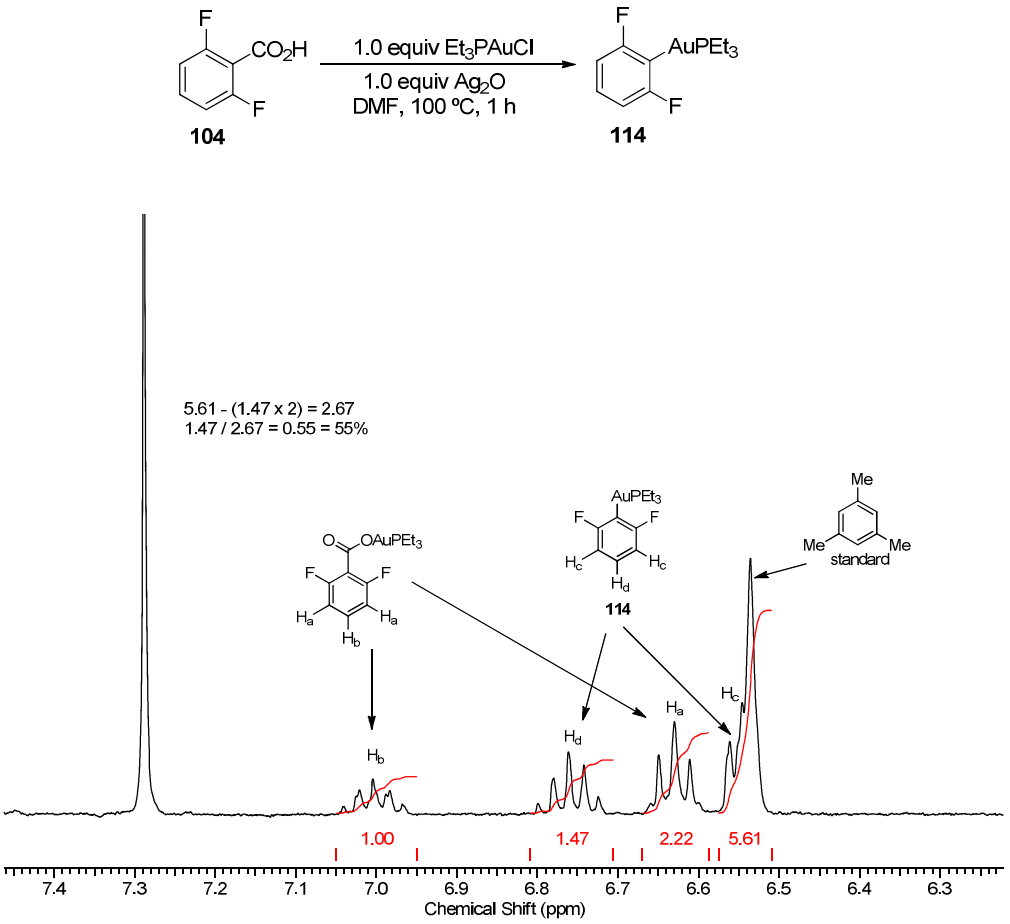
8.6. Experimental Chapter 6

8.6.1. Optimisation of the Au(I)-mediated decarboxylative auration of (hetero)aromatic carboxylic acids

8.6.1.1. General procedure for the optimisation of the Au(I)-mediated decarboxylative auration of (hetero)aromatic carboxylic acids

A mixture of ^{t}Bu$_3$PAuCl (8.7 mg, 0.03 mmol) and potassium 2,6-difluorobenzoate (5.9 mg, 0.03 mmol) in 0.3 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Mesitylene (1 mL 0.01 M, 0.01 mmol) was added and the crude was analysed by ^{1}H NMR.

A ^{1}H NMR of the crude of the reaction described in Table 27, entry 4 but for 1 h is shown below.



8.6.1.2. Effect of the Au(I) salt.

The reactions were carried out following the general procedure but adding different Au(I) salts as described in Table 25.

8.6.1.3. Effect of the AgTFA

The reaction was carried out following the general procedure but adding different 1 equiv of **110** and 1 equiv of AgTFA as described in Scheme 124.

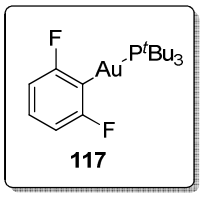
8.6.1.4. Effect of the solvent

The reaction was carried out following the general procedure but adding different 1 equiv of **104** and 1 equiv of Ag_2O using different solvents as described in Table 26.

8.6.1.5. Effect of the temperature

The reaction was carried out following the general procedure but adding different 1 equiv of **104**, 1 equiv of different Au(I) salts and 1 equiv of Ag_2O at different temperatures as described in Table 27.

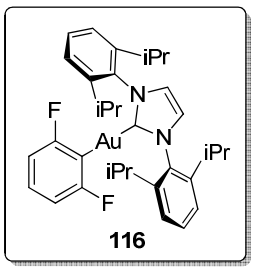
8.6.2. 2,6-Difluorophenyl(tri-*tert*-butylphosphine)gold(I)



117

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 2,6-difluorobenzoic acid (9.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 2 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **117** as a white solid (28.2 mg, 94%); m.p. 126–128 °C; R_f 0.25 (hexanes); IR: 1433, 1200, 1172, 950, 778; ^{1}H NMR (400 MHz) δ 6.95–6.93 (m, 1H), 6.76 (dt, 2H, *J* = 5.4, 2.3 Hz), 1.50 (d, 27H, *J* = 13.0 Hz); ^{13}C NMR (101 MHz) δ 168.6 (ddd, *J* = 231.0, 24.7, 3.7 Hz), 127.4 (t, *J* = 8.4 Hz), 109.7 (dt, *J* = 30.8, 2.9 Hz), 39.2 (d, *J* = 16.1 Hz), 32.5 (d, *J* = 4.6 Hz); ^{31}P NMR (162 MHz) δ 92.21 (t, *J* = 6.4 Hz); ^{19}F NMR (376 MHz) δ –88.31 (d, 2F, *J* = 6.0 Hz); HRMS (EI) calcd. $C_{18}H_{30}AuF_2P$: (M^+), 512.1214; found: (M^+), 512.1214.

8.6.3. [*N*,*N*-Bis(2,6-diisopropylphenyl)imidazol-2-yl](2,6-difluorophenyl)gold(I)

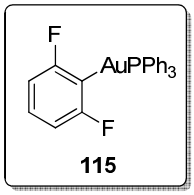


116

A mixture of IPrAuCl (37.3 mg, 0.06 mmol), 2,6-difluorobenzoic acid (9.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 2 h. After this time the reaction mixture was filtered through cotton wool, washed with

CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **116** as a white solid (41.1 mg, 98%); m.p. 271–273 ºC; R_f 0.29 (hexanes); IR: 1434, 1200, 953; ^{1}H NMR (400 MHz) δ 7.48 (t, 2H, *J* = 7.8 Hz), 7.29 (d, 4H, *J* = 7.8 Hz), 7.18 (s, 2H), 6.84–6.77 (m, 1H), 6.58 (dd, 2H, *J* = 7.7, 5.3 Hz), 2.67 (spt, 4H, *J* = 6.8 Hz), 1.40 (d, 12H, *J* = 6.8 Hz), 1.25 (d, 12H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz) δ 194.3, 169.0 (dd, *J* = 231.7, 25.1 Hz), 145.8, 134.4, 130.27, 126.2 (t, *J* = 8.1 Hz), 123.9, 122.8, 109.0 (dd, *J* = 31.0, 3.2 Hz), 28.9, 24.3, 24.0; ^{19}F NMR (376 MHz) δ –88.35 (s, 2F); HRMS (ESI) calcd. $C_{33}H_{41}AuF_2N_2$: ($[M+H]^+$), 700.2898; found: ($[M+H]^+$), 700.2850.

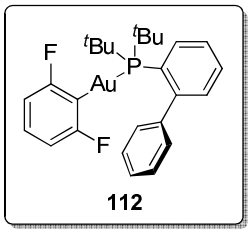
8.6.4. 2,6-Difluorophenyl(triphenylphosphine)gold(I)



115

A mixture of Ph_3PAuCl (29.7 mg, 0.06 mmol), 2,6-difluorobenzoic acid (9.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 2 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **115** as a transparent oil (32.6 mg, 95%); R_f 0.27 (hexanes); IR: 1434, 1202, 1101, 952, 694, 686; ^{1}H NMR (400 MHz) δ 7.65–7.60 (m, 6H), 7.54–7.46 (m, 9H), 7.12–7.04 (m, 1H), 7.89 (dd, 2H, *J* = 7.9, 5.5 Hz); ^{13}C NMR (101 MHz) δ 168.5 (dd, *J* = 231.5, 23.7 Hz), 134.4 (d, *J* = 13.9 Hz), 131.4, (d, *J* = 10.1 Hz), 130.5 (d, *J* = 51.7 Hz), 129.1 (d, *J* = 11.0 Hz), 127.9 (t, *J* = 8.6 Hz), 110.0 (dd, *J* = 30.6, 3.3 Hz); ^{31}P NMR (162 MHz) δ 43.35 (t, 1P, *J* = 8.1 Hz); ^{19}F NMR (376 MHz) δ –88.95 (d, 2F, *J* = 7.5 Hz); HRMS (EI) calcd. $C_{24}H_{18}AuF_2P$ (M^+), 572.0780; found: (M^+), 572.0782.

8.6.5. 2,6-Difluorophenyl[(2-biphenyl)di-*tert*-butylphosphine]gold(I)



112

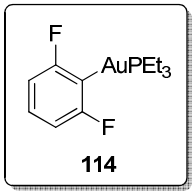
From $^{t}Bu_2$biphenPAuCl:

A mixture of $^{t}Bu_2$biphenPAuCl (31.8 mg, 0.06 mmol), 2,6-difluorobenzoic acid (9.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **112** as a white solid (34.1 mg, 94%); m.p. 180–182 ºC; R_f 0.29 (hexanes); IR: 1436, 1023, 956, 773, 757, 699; ^{1}H NMR (400 MHz) δ 7.94–7.90 (m, 1H), 7.50–7.47 (m, 2H), 7.29–7.26 (m, 1H), 7.22–7.15 (m, 4H), 6.97–6.91 (m, 1H), 6.79–6.71 (m, 3H), 1.48 (d, 18H, *J* = 14.7 Hz); ^{13}C NMR (101 MHz) δ 168.1 (ddd, *J* = 230.2, 24.8, 3.8 Hz), 150.5 (d, *J* = 16.1 Hz), 142.5 (d, *J* = 6.0 Hz), 134.7, 132.9 (d, *J* = 7.4 Hz), 130.0, 128.8, 128.4, 128.0 (d, *J* = 36.2 Hz), 127.0, 126.4 (d, *J* = 5.6 Hz), 126.3 (t, *J* = 8.3 Hz), 109.2 (dt, *J* = 31.5, 3.0 Hz), 37.6 (d, *J* = 20.7 Hz), 31.0 (d, *J* = 7.2 Hz); ^{31}P NMR (162 MHz) δ 65.55 (t, 1P, *J* = 6.4 Hz); ^{19}F NMR (376 MHz) δ –88.13 (d, 2F, *J* = 7.5 Hz); HRMS (ESI) calcd. $C_{26}H_{30}AuF_2PNa$ ($[M+Na]^+$), 631.1611; found: ($[M+Na]^+$) 631.1606.

From [Au($^{t}Bu_2$biphenP)(MeCN)]SbF_6:

A mixture of [Au($^{t}Bu_2$biphenP)(MeCN)]SbF_6 (46.2 mg, 0.06 mmol) and potassium 2,6-difluorobenzoate (11.8 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 6 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **112** as a white solid (33.0 mg, 92%).

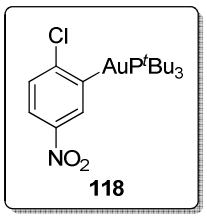
8.6.6. 2,6-Difluorophenyl(triethylphosphine)gold(I)



114

A mixture of Et_3PAuCl (21.0 mg, 0.06 mmol), 2,6-difluorobenzoic acid (9.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **114** as a transparent oil (25.0 mg, 97%); R*f* 0.23 (hexanes); IR: 1433, 1201, 953, 771; ^{1}H NMR (400 MHz) δ 7.07–7.00 (m, 1H), 6.86–6.83 (m, 2H), 1.93–1.85 (m, 6H), 1.27 (dt, 9H, *J* = 18.0, 7.6 Hz); ^{13}C NMR (101 MHz) δ 168.7 (ddd, *J* = 231.2, 25.6, 4.2 Hz), 127.6 (t, *J* = 8.6 Hz), 109.7 (dt, *J* = 30.9, 3.3 Hz), 18.1 (d, *J* = 31.2 Hz), 9.0; ^{31}P NMR (162 MHz) δ 40.7 (t, 1P, *J* = 8.1 Hz); ^{19}F NMR (376 MHz) δ –89.45 (d, 2F, *J* = 8.3 Hz); HRMS (EI) calcd. $C_{12}H_{18}AuF_2P$ (M^+), 428.0780; found: (M^+), 428.0767.

8.6.7. 2-Chloro-5-nitrophenyl(tri-*tert*-butylphosphine)gold(I)

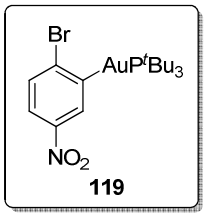


118

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 2-chloro-5-nitrobenzoic acid (12.1 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes:EtOAc 9:1) afforded compound **118** as a white solid (29.5 mg, 96%); m.p. 152–154 ºC; R_f 0.60 (hexanes:EtOAc 9:1); IR: 1513, 1337, 1277, 1024; ^{1}H NMR (400 MHz) δ 8.31 (dd, 1H, *J* = 5.0, 2.9 Hz), 7.81 (dd, 1H, *J* = 8.7, 2.9 Hz), 7.43 (dd, 1H, *J* = 8.7, 1.72 Hz), 1.58 (d, 27H, *J* = 13.0 Hz); ^{13}C NMR (101 MHz) δ 177.7 (d, *J* = 104.4 Hz), 151.2 (d, *J* = 2.8 Hz), 146.1, 134.3,

127.8 (d, *J* = 4.1 Hz), 121.4, 39.1 (d, *J* = 15.6 Hz), 32.4 (d, *J* = 4.5 Hz); ^{31}P NMR (162 MHz) δ 91.34 (s, 1P); HRMS (ESI) calcd. $C_{18}H_{31}AuClNO_2P$: ($[M+H]^+$), 556.1441; found: ($[M+H]^+$), 556.1434.

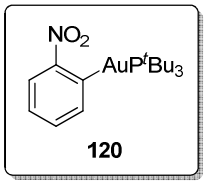
8.6.8. 2-Bromo-5-nitrophenyl(tri-*tert*-butylphosphine)gold(I)



119

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 2-bromo-5-nitrobenzoic acid (14.7 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 2 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **119** as a white solid (26 mg, 72%); m.p. 179–181 ºC; R_f 0.36 (hexanes); IR: 1510, 1329, 864, 811, 738; 1H NMR (400 MHz) δ 8.18 (dd, 1H, *J* = 4.8, 2.8 Hz), 7.71 (dd, 1H, *J* = 8.6, 2.8 Hz), 7.60 (dd, 1H, *J* = 8.7, 1.4 Hz), 1.59 (d, 27H, *J* = 13.0 Hz); 13C NMR (101 MHz) δ 180.7 (d, *J* = 105.0 Hz), 145.5 (d, *J* = 6.1 Hz), 141.8 (d, *J* = 2.9 Hz), 133.6, 130.0 (d, *J* = 4.4 Hz), 120.5, 38.1 (d, *J* = 15.5 Hz), 31.4 (d, *J* = 4.4 Hz); ^{31}P NMR (162 MHz) δ 91.01 (s, 1P); HRMS(EI) calcd. $C_{18}H_{31}AuBrNO_2P$: ($[M+H]^+$), 600.0936; found: ($[M+H]^+$), 600.0933.

8.6.9. 2-Nitrophenyl(tri-*tert*-butylphospine)gold(I)

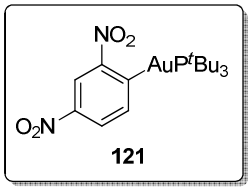


120

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 2-nitrobenzoic acid (11.8 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **120** as a yellow solid (24.4 mg, 78%);

m.p. 132–134 ºC; R_f 0.13 (hexanes); IR: 1483, 1335, 1175, 728; ^{1}H NMR (400 MHz) δ 8.06 (d, 1H, *J* = 8.3 Hz), 7.69–7.67 (m, 1H), 7.46 (td, 1H, *J* = 7.2, 0.7 Hz), 7.18 (td, 1H, *J* = 7.2, 1.1 Hz); ^{13}C NMR (101 MHz) δ 169.8 (d, *J* = 102.1 Hz), 157.8, 140.6 (d, *J* = 1.8 Hz), 132.0 (d, *J* = 4.2 Hz), 125.3, 123.5 (d, *J* = 3.6 Hz), 38.8 (d, *J* = 15.7 Hz), 32.4 (d, *J* = 4.7 Hz); ^{31}P NMR (162 MHz) δ 92.11 (s, 1P); HRMS (ESI) calcd. $C_{18}H_{31}AuNNaO_2P$: ([M+Na]$^+$), 544.1650; found: ([M+Na]$^+$), 544.1646.

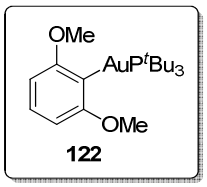
8.6.10. 2,4-Dinitrophenyl(tri-*tert*-butylphosphine)gold(I)



121

A mixture of ^{t}Bu$_3$PAuCl (8.71 mg, 0.02 mmol), 2,4-dinitrobenzoic acid (4.24 mg, 0.02 mmol) and Ag_2O (4.63 mg, 0.02 mmol) in 0.3 mL of DMF was stirred at 100 ºC for 4 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **121** as a yellow solid (9.17 mg, 81%); m.p. 209–211 ºC; R_f 0.39 (hexanes); IR: 1579, 1509, 1339, 1173, 906, 834; ^{1}H NMR (400 MHz) δ 8.90 (m, 1H), 8.25 (dd, 1H, *J* = 8.0, 2.1 Hz), 7.86 (dd, 1H, *J* = 8.0, 3.9 Hz), 1.58 (dd, 27H, *J* = 13.2 Hz); ^{13}C NMR (101 MHz) δ 180.0 (d, *J* = 100.8 Hz), 157.2, 145.7, 141.7, 125.0 (d, *J* = 3.9 Hz), 118.4 (d, *J* = 3.7 Hz), 39.0 (d, *J* = 16.6 Hz), 32.4 (d, *J* = 4.5 Hz); ^{31}P NMR (162 MHz) δ 91.75 (s, 1P); HRMS (ESI) calcd. $C_{18}H_{30}AuN_2O_4P$: ([M+H]$^+$), 567.1681; found: ([M+H]$^+$), 567.1675.

8.6.11. 2,6-Dimethoxyphenyl(tri-*tert*-butylphosphine)gold(I)

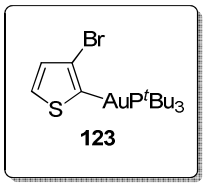


122

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 2,6-dimethoxybenzoic acid (10.9 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 2 h. After this time the reaction mixture was filtered through cotton wool, washed

with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes:EtOAc 8:2) afforded compound **122** as a white solid (24.1 mg, 75%); m.p. 146–148 ºC; R_f 0.27 (hexanes:EtOAc 8:2); IR: 1567, 1449, 1220, 1096, 709; ^{1}H NMR (400 MHz) δ 7.04 (t, 1H, *J* = 8.0 Hz), 6.63 (dd, 2H, *J* = 8.0, 1.9 Hz), 3.81 (s, 6H), 1.58 (d, 27H, *J* = 12.7 Hz); ^{13}C NMR (101 MHz) δ 166.9, 148.0 (d, *J* = 96.4 Hz), 127.0 ,105.8 (d, *J* = 3.6 Hz), 56.4, 38.9 (d, *J* = 14.5 Hz), 32.4 (d, *J* = 4.8 Hz); ^{31}P NMR (162 MHz) δ 93.03 (s, 1P); HRMS (ESI) calcd. $C_{20}H_{36}AuO_2P$: ($[M+H]^+$), 537.2197; found: ($[M+H]^+$), 537.2181.

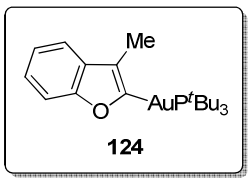
8.6.12. 3-Bromothiophen-2-yl(tri-*tert*-butylphosphine)gold(I)



123

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 3-bromothiophene-2-carboxylic acid (12.4 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **123** as a white solid (29.3 mg, 87%); m.p. 181–183 ºC; R*f* 0.34 (hexanes); IR: 1469, 1392, 1318, 1172, 844, 700; ^{1}H NMR (400 MHz) δ 7.38 (dd, 1H, *J* = 4.8, 2.0 Hz), 7.24 (dd, 1H, *J* = 4.8, 0.9 Hz), 1.58 (d, 27H, *J* = 13.1 Hz); ^{13}C NMR (101 MHz) δ 169.4 (d, *J* = 111.8 Hz); 130.1 (d, *J* = 5.2 Hz), 128.5 (d, *J* = 3.4 Hz), 115.7, 39.2 (d, *J* = 16.2 Hz), 32.4 (d, *J* = 4.5 Hz); ^{31}P NMR (162 MHz) δ 90.80 (s, 1P); HRMS (ESI) calcd. $C_{16}H_{29}AuBrNaPS$: ($[M+Na]^+$), 583.0469; found: ($[M+Na]^+$), 583.0464.

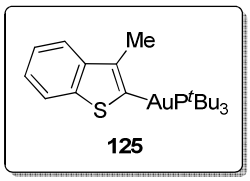
8.6.13. 3-Methylbenzo[*b*]furan-2-yl(tri-*tert*-butylphosphine)gold(I)



124

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 3-methylbenzo[*b*]furan-2-carboxylic acid (10.6 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **124** as a white solid (25.4 mg, 80%); m.p. 170–172 ºC; R_f 0.41 (hexanes); IR: 1441, 1227, 1172, 1009, 707; ^{1}H NMR (400 MHz) δ 7.42–7.38 (m, 2H), 7.15–7.08 (m, 2H), 2.38 (s, 3H), 1.60 (d, 27H, *J* = 13.0 Hz); ^{13}C NMR (101 MHz) δ 199.5 (d, *J* = 123.3 Hz), 158.4, 130.2, 123.1 (d, *J* = 8.1 Hz), 121.5, 120.8, 118.1, 110.2, 39.1 (d, *J* = 16.1 Hz), 32.5 (d, *J* = 5.0 Hz), 9.9; ^{31}P NMR (162 MHz) δ 92.45 (s, 1P); HRMS (EI) calcd. $C_{21}H_{34}AuPO$ (M^+), 530.2007; found: (M^+), 530.1986.

8.6.14. 3-Methylbenzo[*b*]thiophen-2-yl(tri-*tert*-butylphosphine)gold(I)

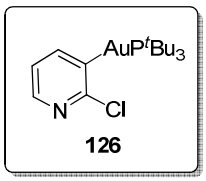


125

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 3-methylbenzo[*b*]thiophene-2-carboxylic acid (11.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **125** as a white solid (28.0 mg, 85%); m.p. 161–163 ºC; R_f 0.37 (hexanes); IR: 1172, 754, 731; ^{1}H NMR (400 MHz) δ 7.79 (d, 1H, *J* = 7.9 Hz), 7.64 (d, 1H, *J* = 7.9 Hz), 7.29 (t, 1H, *J* = 6.9 Hz), 7.19 (t, 1H, *J* = 6.9 Hz), 2.60 (s, 3H), 1.60 (d, 27H, *J* = 12.9 Hz); ^{13}C NMR (101 MHz) δ 144.5, 141.8, 135.8, 121.6, 121.5, 120.8, 39.1 (d, *J* =

15.1 Hz), 32.5 (d, J = 4.1 Hz), 17.6; ^{31}P NMR (162 MHz) δ 92.58 (s, 1P); HRMS (EI) calcd. $C_{21}H_{34}AuPS$ (M^+), 546.1784; found: (M^+), 546.1613.

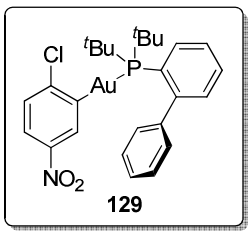
8.6.15. 2-Chloropyridin-3-yl(tri-*tert*-butylphosphine)gold(I)



126

A mixture of ^{t}Bu$_3$PAuCl (26.1 mg, 0.06 mmol), 2-chloronicotinic acid (9.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **126** as a white solid (21.5 mg, 70%); m.p. 174–176 ºC; R_f 0.20 (hexanes); IR: 1353, 1102, 1049, 1025, 787, 737; ^{1}H NMR (400 MHz) δ 8.04 (dd, 1H, J = 4.6, 2.1 Hz), 7.74–7.70 (m, 1H), 7.04 (ddd, 1H, J = 7.0, 4.7, 0.7 Hz), 1.57 (d, 27H, J = 13.0 Hz); ^{13}C NMR (101 MHz) δ 170.8 (d, J = 105.4 Hz), 161.5, 149.1, 145.9, 121.7 (d, J = 3.7 Hz); ^{31}P NMR (162 MHz) δ 91.73 (s, 1P); HRMS (ESI) calcd. $C_{17}H_{31}AuClNP$: ($[M+H]^+$), 512.1543; found: ($[M+H]^+$), 512.1536.

8.6.16. 2-Chloro-5-nitrophenyl[(tri-*tert*-butyl)(2-biphenyl)phosphine]gold(I)



129

From ^{t}Bu$_2$biphenPAuCl:

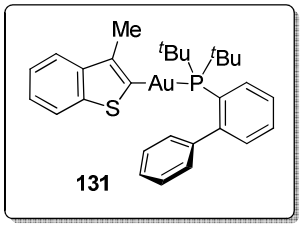
A mixture of ^{t}Bu$_2$biphenPAuCl (31.8 mg, 0.06 mmol), 2-chloro-5-nitrobenzoic acid (12.0 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 5 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **129** as a white solid

(27.6 mg, 73%); m.p. 136–138 ºC; R_f 0.36 (hexanes); IR: 1585, 1334, 1022, 903, 868, 771, 744; ^{1}H NMR (400 MHz) δ 7.95–7.91 (m, 1H), 7.82 (dd, 1H, *J* = 5.2, 2.8 Hz), 7.74 (dd, 1H, *J* = 8.8, 3.2 Hz), 7.53–7.46 (m, 2H), 7.33–7.18 (m, 6H), 6.98–6.94 (m, 1H), 1.48 (d, 18H, *J* = 14.8 Hz); ^{13}C NMR (101 MHz) δ 175.0 (d, *J* = 107.0 Hz), 150.9 (d, *J* = 2.7 Hz), 150.3 (d, *J* = 15.8 Hz), 145.5 (d, *J* = 6.0 Hz), 143.0 (d, *J* = 5.8 Hz), 134.7, 134.3, 133.1 (d, *J* = 7.6 Hz), 130.1 (d, *J* = 1.9 Hz), 129.3, 128.3, 128.0 (d, *J* = 36.4 Hz), 127.4, 127.3 (d, *J* = 4.2 Hz), 126.5 (d, *J* = 5.5 Hz), 120.7, 37.6 (d, *J* = 20.4 Hz), 31.0 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz) δ 64.46 (s, 1P); HRMS (ESI) calcd. $C_{26}H_{31}AuClNO_2P$ ($[M+H]^+$), 652.1441; found: ($[M+H]^+$) 652.1438.

From [Au(^{t}Bu$_2$biphenP)(MeCN)]SbF_6:

A mixture of [Au(^{t}Bu$_2$biphenP)(MeCN)]SbF_6 (46.2 mg, 0.06 mmol) and potassium 2-chloro-5-nitrobenzoate (14.4 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 110 ºC for 8 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **129** as a white solid (29.2 mg, 74%).

8.6.17. 3-Methylbenzo[*b*]thiophen-2-yl[(tri-*tert*-butyl)(2-biphenyl) phosphine] gold(I)



131

From (^{t}Bu$_2$biphen)PAuCl:

A mixture of (^{t}Bu$_2$biphen)PAuCl (31.8 mg, 0.06 mmol), 3-methylbenzo[*b*]thiophene-2-carboxylic acid (11.5 mg, 0.06 mmol) and Ag_2O (13.9 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **131** as a white solid (31.2 mg, 79%); m.p. 182–184 ºC R_f 0.27 (hexanes); IR: 1468, 1172, 901, 773; 1H NMR (400 MHz) δ 7.96–7.92 (m, 1H), 7.77 (d, 1H, *J* = 8.1 Hz),

7.58 (d, 1H, *J* = 8.1 Hz), 7.51–7.47 (m, 2H), 7.36–7.14 (m, 7H), 7.07–7.03 (m, 1H), 2.39 (s, 3H), 1.50 (d, 18H, *J* = 14.8 Hz); 13C NMR (101 MHz) δ 168.0 (d, *J* = 115.1 Hz), 150.5 (d, *J* = 16.1 Hz), 144.5 (d, *J* = 3.6 Hz), 142.2 (d, *J* = 6.0 Hz), 141.6 (d, *J* = 6.7 Hz), 134.8, 134.4, 132.8 (d, *J* = 7.3 Hz), 130.1, 128.9, 128.5, 128.3, 127.9 (d, *J* = 35.0 Hz), 126.5 (d, *J* = 5.3 Hz), 122.2, 121.4, 120.9, 120.4, 37.7 (d, *J* = 20.5 Hz), 31.1 (d, *J* = 6.9 Hz), 17.7; 31P NMR (162 MHz) δ 65.37 (s, 1P).

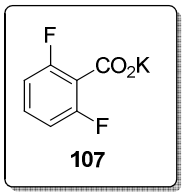
From [Au(^{t}Bu$_2$biphenP)(MeCN)]SbF$_6$:

A mixture of [Au(^{t}Bu$_2$biphenP)(MeCN)]SbF$_6$ (46.2 mg, 0.06 mmol) and potassium 3-methylbenzo[*b*]thiophene-2-carboxylate (13.8 mg, 0.06 mmol) in 0.9 mL of DMF was stirred at 100 ºC for 3 h. After this time the reaction mixture was filtered through cotton wool, washed with CH_2Cl_2 and evaporated to dryness. Column chromatography on deactivated (2% Et_3N) silica gel (hexanes) afforded compound **131** as a white solid (36.4 mg, 93%).

8.6.18. General procedure for the synthesis of potassium carboxylates

According to the literature,[108] a solution of ^{t}BuOK (2.0 mmol) in EtOH (5 mL) was added dropwise to a solution of aromatic acid (0.224 g, 2.0 mmol) in EtOH (5 mL) at room temperature. After 1 h, part of the solvent was removed and 20 mL of Et_2O were added. The mixture was filtered and washed with cold EtOH and cold Et_2O. The resulting solid was dried under high vacuum at 50 ºC for 5 h affording the corresponding potassium salts.

8.6.18.1. Potassium 2,6-difluorobenzoate[109]

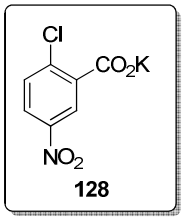


107

The reaction was performed according to the general procedure with 2,6-difluorobenzoic acid (0.230 g, 2 mmol) yielding **107** as a white solid (0.373 g, 95%); IR: 1610, 1378, 1006; ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 7.13–7.05 (m, 1H), 6.87–6.83 (m, 1H); ^{13}C NMR (101 MHz, *d*$_6$-DMSO) δ 125.7 (t, *J* = 9.4 Hz), 110.8 (dd, *J* =

19.6, 7.3 Hz); HRMS (ESI) calcd. $C_7H_3F_2O_2$: ([M–K]$^-$), 157.0107; found: ([M–K]$^-$), 157.0107.

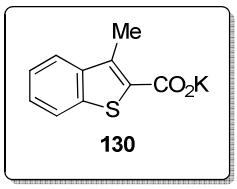
8.6.18.2. Potassium 2-chloro-5-nitrobenzoate



128

The reaction was performed according to the general procedure with 2-chloro-5-nitrobenzoic acid (0.403 g, 2 mmol) yielding **128** as a white solid (0.445 g, 93%); IR: 1597, 1341, 1046; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.09 (d, 1H, J = 2.8 Hz), 7.96 (dd, 1H, J = 8.7, 2.8 Hz), 7.55 (d, 1H, J = 8.7 Hz); ^{13}C NMR (101 MHz, d_6-DMSO) δ 165.7, 145.8, 145.4, 136.2, 130.4, 122.9, 121.6; HRMS (ESI) calcd. $C_7H_3ClNO_4$: ([M–K]$^-$), 199.9756; found: ([M–K]$^-$), 199.9795.

8.6.18.3. Potassium 3-methylbenzo[b]thiophen-2-carboxylate



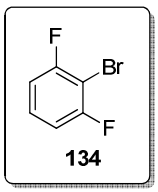
130

The reaction was performed according to the general procedure with 3-methylbenzo[*b*]thiophene-2-carboxylic acid (0.384 g, 2 mmol) yielding **130** as a white solid (0.391 g, 85%); IR: 1559, 1374, 1314; ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.78–7.76 (m, 1H), 7.68–7.66 (m, 1H), 7.33–7.29 (m, 2H), 2.64 (s, 3H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 141.7, 138.4, 129.4, 124.1, 123.1, 122.1, 122.0, 11.9. HRMS (ESI) calcd. $C_{10}H_7O_2S$: ([M–K]$^-$), 191.0172; found: ([M–K]$^-$), 191.0170.

8.6.19. Gold(I)-mediated decarboxylative halogenations

All the products were commercially available or previously reported. The spectroscopic data matched with those reported in the literature.

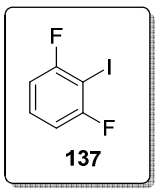
8.6.19.1. 2-Bromo-1,3-difluorobenzene



134

A mixture of 2,6-difluorobenzoic acid (0.02 mmol, 3.2 mg), Ag_2O (0.02 mmol, 4.6 mg) and $^tBu_3PAuCl$ (0.02 mmol, 8.7 mg) in DMF (0.3 mL) was stirred for 3 h at 100 ºC. After this time, the mixture was cooled to 50 ºC and NBS (0.022 mmol, 3.9 mg) were added and stirred for another hour. The reaction was filtered through cotton wool affording 98% NMR yield of **134** using mesitylene as internal standard. CAS: [64248-56-2]

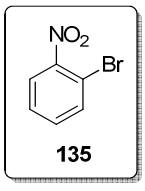
8.6.19.2. 1,3-Difluoro-2-iodobenzene[110]



137

A mixture of 2,6-difluorobenzoic acid (0.02 mmol, 3.2 mg), Ag_2O (0.02 mmol, 4.6 mg) and $^tBu_3PAuCl$ (0.02 mmol, 8.7 mg) in DMF (0.3 mL) was stirred for 3 h at 100 ºC. After this time, the mixture was cooled to 50 ºC and NIS (0.022 mmol, 4.9 mg) were added and stirred for another hour. The reaction was filtered through cotton wool affording 97% NMR yield of **137** using mesitylene as internal standard.

8.6.19.3. 1-Bromo-2-nitrobenzene

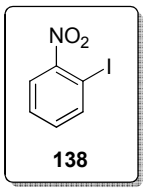


135

A mixture of 2-nitrobenzoic acid (0.02 mmol, 3.3 mg), Ag_2O (0.02 mmol, 4.6 mg) and $^tBu_3PAuCl$ (0.02 mmol, 8.7 mg) in DMF (0.3 mL) was stirred for 2 h at 110 ºC. After this time, the mixture was cooled to 50 ºC and NBS (0.022 mmol, 3.9 mg) were

added and stirred for another hour. The reaction was filtered through cotton wool affording 62% NMR yield of **135** using mesitylene as internal standard. CAS: [577-19-5]

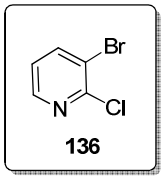
8.6.19.4. 1-Iodo-2-nitrobenzene



138

A mixture of 2-nitrobenzoic acid (0.02 mmol, 3.3 mg), Ag_2O (0.02 mmol, 4.6 mg) and $^tBu_3PAuCl$ (0.02 mmol, 8.7 mg) in DMF (0.3 mL) was stirred for 2 h at 110 ºC. After this time, the mixture was cooled to 50 ºC and NIS (0.022 mmol, 4.9 mg) were added and stirred for another hour. The reaction was filtered through cotton wool affording 82% NMR yield of **138** using mesitylene as internal standard. CAS: [609-73-4]

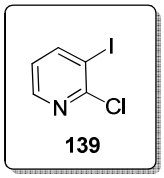
8.6.19.5. 3-Bromo-2-chloropyridine



136

A mixture of 2-chloropyridine-3-carboxylic acid (0.02 mmol, 3.1 mg), Ag_2O (0.02 mmol, 4.6 mg) and $^tBu_3PAuCl$ (0.02 mmol, 8.7 mg) in DMF (0.3 mL) was stirred for 3 h at 110 ºC. After this time, the mixture was cooled to 50 ºC and NBS (0.022 mmol, 3.9 mg) were added and stirred for another hour. The reaction was filtered through cotton wool affording 71% NMR yield of **136** using mesitylene as internal standard. CAS: [52200-48-3]

8.6.19.6. 2-Chloro-3-iodopyridine



139

A mixture of 2-chloropyridine-3-carboxylic acid (0.02 mmol, 3.1 mg), Ag_2O (0.02 mmol, 4.6 mg) and $^tBu_3PAuCl$ (0.02 mmol, 8.7 mg) in DMF (0.3 mL) was stirred for 3 h at 110 ºC. After this time, the mixture was cooled to 50 ºC and NIS (0.022 mmol, 4.9 mg) were added and stirred for another hour. The reaction was filtered through cotton wool affording 68% NMR yield of **139** using mesitylene as internal standard. CAS: [78607-36-0]

8.6.20. Analysis of Ag(I) ions by Atomic Absorbance Spectroscopy

The content in silver in $^tBu_2$biphenPAuSbF$_6$:MeCN and the K-carboxylate **128** was determined by Atomic Absorption analysis.

Standards

Solution A (600 mg Ag/L): 9.44 mg of $AgNO_3$ were dissolved in 10 mL of distilled H_2O in a volumetric flask.

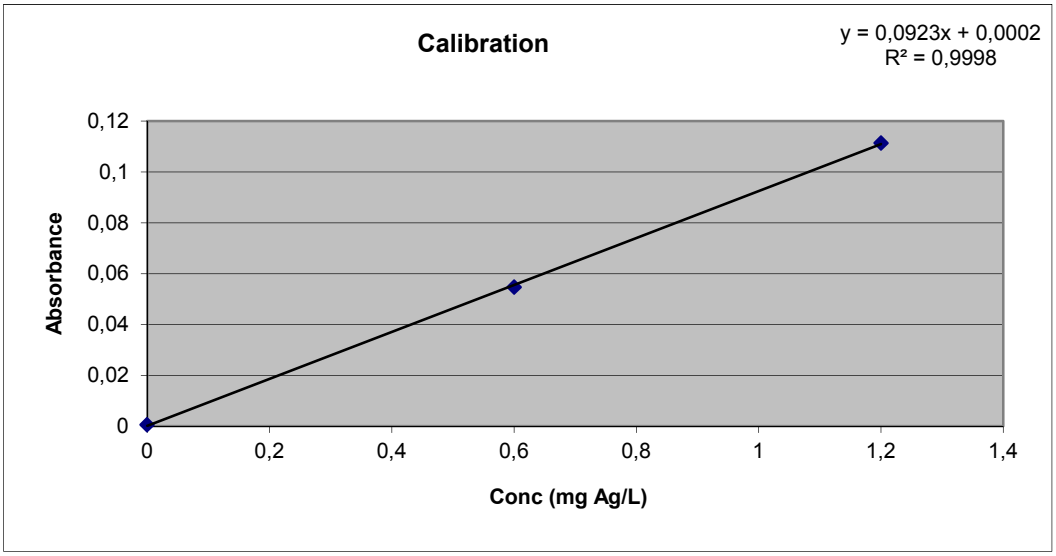
Solution 1 (0.6 mg Ag/L): a 50 mL stock solution was prepared with 0.05 mL of solution A and 2 mL of analytically pure HNO_3 14 M in H_2O.

Solution 2 (1.2 mg Ag/L): a 50 mL stock solution was prepared with 0.10 mL of solution A and 2 mL of analytically pure HNO_3 14 M in H_2O.

Samples

Sample 1: a solution of 10 mg of $^tBu_2$biphenPAuSbF$_6$:MeCN in 0.5 mL of analytically pure HNO_3 14 M was heated overnight at 80 ºC in a test tube. After this time the sample was diluted up to 10 mL with H_2O in a volumetric flask.

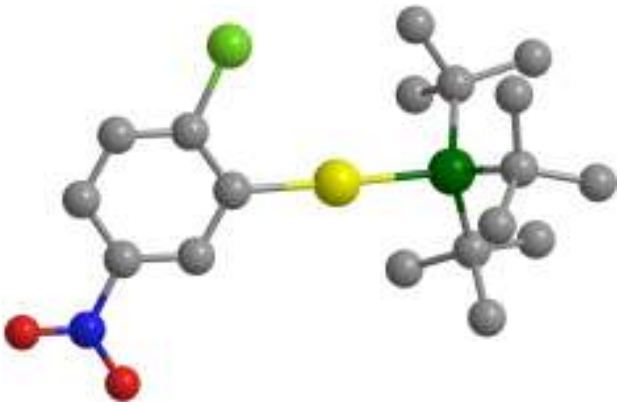
Sample 2: a 10 mL stock solution was prepared dissolving 10 mg of potassium 2-chloro-5-nitrobenzoate (**128**) in H_2O.



Sample	Absorbance	Conc mg/L	mmol/mL	% Ag sample
1	0.0013	0.0119	1.10E-07	0.0085
2	0.0042	0.0433	4.02E-07	0.0096

8.6.21. Crystallographic data

Crystallographic data: X-ray diffraction studies for **118, 123** and **126** were performed at 93K using a Rigaku MM007/ Mercury/ diffractometer (confocal optics Mo-Kα radiation). Intensity data were collected using ω steps accumulating area detector frames spanning at least a hemisphere of reciprocal space for all structures (data were integrated using CrystalClear). All data were corrected for Lorentz, polarisation and long-term intensity fluctuations. Absorption effects were corrected on the basis of multiple equivalent reflections. Structures were solved by direct methods and refined by full-matrix least-squares against F^2 (SHELXTL). All hydrogen atoms were assigned riding isotropic displacement parameters and constrained to idealised geometries.

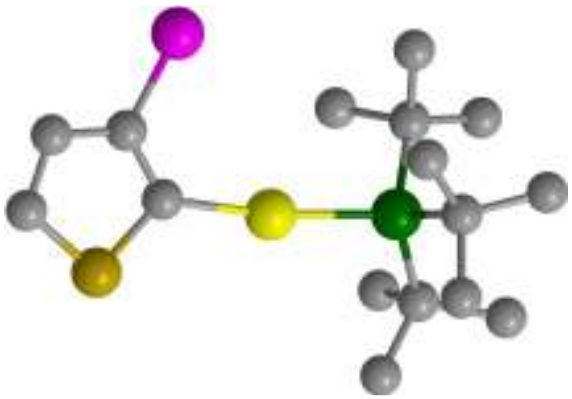


X-ray crystal structure of **118**.

*8.6.22.1. Crystal data and structure refinement for **118**.*

Identification code	4C	
CCDC	CCDC 777054	
Empirical formula	C18 H30 Au Cl N O2 P	
Formula weight	555.82	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 19.273(5) Å	α= 90°.
	b = 8.5945(18) Å	β= 99.383(8)°.
	c = 25.128(7) Å	γ = 90°.
Volume	4106.5(18) $Å^3$	
Z	8	
Density (calculated)	1.798 Mg/m^3	
Absorption coefficient	7.383 mm^{-1}	
F(000)	2176	
Crystal size	0.10 x 0.06 x 0.06 mm^3	
Theta range for data collection	2.14 to 25.32°.	
Index ranges	-23<=h<=23, -10<=k<=10, -30<=l<=20	
Reflections collected	24949	
Independent reflections	7458 [R(int) = 0.0512]	
Completeness to theta = 25.00°	99.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.000 and 0.733	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	7458 / 0 / 434
Goodness-of-fit on F^2	1.119
Final R indices [I>2sigma(I)]	R1 = 0.0447, wR2 = 0.0942
R indices (all data)	R1 = 0.0576, wR2 = 0.1004
Largest diff. peak and hole	4.142 and -1.798 e.Å^{-3}

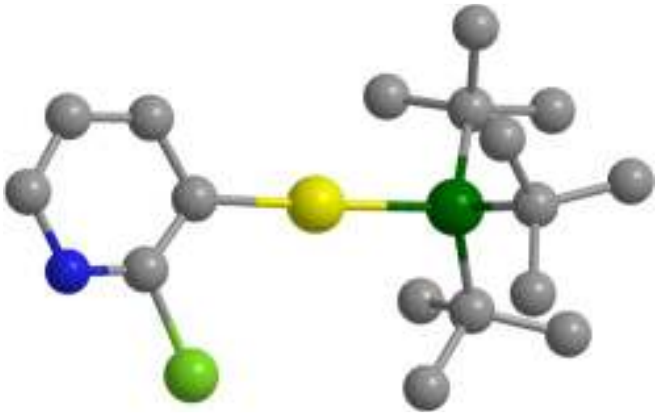


X-ray crystal structure of **123**.

*8.6.22.2. Crystal data and structure refinement for **123**.*

Identification code	4G	
CCDC	CCDC 777055	
Empirical formula	C16 H29 Au Br P S	
Formula weight	561.30	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.132(5) Å	α= 90°.
	b = 14.201(6) Å	β= 114.238(10)°.
	c = 12.261(6) Å	γ = 90°.
Volume	1926.3(14) Å^3	
Z	4	
Density (calculated)	1.935 Mg/m^3	
Absorption coefficient	9.894 mm^{-1}	
F(000)	1080	
Crystal size	0.15 x 0.03 x 0.03 mm^3	
Theta range for data collection	2.32 to 25.43°.	

Index ranges	-14<=h<=13, -17<=k<=12, -14<=l<=14
Reflections collected	12341
Independent reflections	3522 [R(int) = 0.1204]
Completeness to theta = 25.00°	99.6 %
Absorption correction	Multiscan
Max. and min. transmission	1.000 and 0.468
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3522 / 0 / 182
Goodness-of-fit on F^2	0.806
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.0741
R indices (all data)	R1 = 0.0715, wR2 = 0.0822
Largest diff. peak and hole	1.095 and -1.449 e.Å^{-3}



X-ray crystal structure of **126**.

*8.6.22.3. Crystal data and structure refinement for **126**.*

Identification code	4H	
CCDC	CCDC 777056	
Empirical formula	C17 H30 Au Cl N P	
Formula weight	511.81	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 23.158(5) Å	α= 90°.
	b = 11.068(2) Å	β= 110.066(6)°.
	c = 16.019(3) Å	γ = 90°.

Volume	3856.6(14) $Å^3$
Z	8
Density (calculated)	1.763 Mg/m^3
Absorption coefficient	7.846 mm^{-1}
F(000)	2000
Crystal size	0.10 x 0.10 x 0.02 mm^3
Theta range for data collection	3.14 to 25.37°.
Index ranges	-26<=h<=27, -13<=k<=11, -18<=l<=19
Reflections collected	24174
Independent reflections	6947 [R(int) = 0.0515]
Completeness to theta = 25.00°	98.6 %
Absorption correction	Multiscan
Max. and min. transmission	1.000 and 0.704
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6947 / 0 / 380
Goodness-of-fit on F^2	1.180
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.0718
R indices (all data)	R1 = 0.0476, wR2 = 0.0813
Largest diff. peak and hole	1.262 and -0.967 $e.Å^{-3}$

References

[1] Markham, A.; Goa, K. L. *Drugs*, **2004**, *4*, 395.

[2] Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248.

[3] Matheron, M. E.; Porchas, M. *Plant. Dis*. **2004**, *88*, 665.

[4] Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem. Int. Ed*. **1998**, *37*, 402.

[5] http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/

[6] A person generates an average of 27 kg of CO_2 a day in the UK. http://www.27kilos.com

[7] Shepard, A. F.; Winslow, N. R.; Jonhson, J. R. *J. Am. Chem. Soc.* **1930**, *52*, 2083.

[8] (a) Björklund, C.; Nilsson, M. *Acta. Chem. Scand*. **1968**, *22*, 2585; (b) Chodowska-Palicka, J.; Nilsson, M. *Acta. Chem. Scand*. **1970**, *24*, 3353; (c) Chodowska-Palicka, J.; Nilsson, M. *Acta. Chem. Scand*. **1971**, *25*, 3451.

[9] (a) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189; (b) Cohen, T.; Berninger, R. W.; Wood, J. T. *J. Org. Chem.* **1978**, *43*, 837.

[10] Cairncross, A.; Roland, J. R.; Henderson, R. M.; Sheppard, W. A. *J. Am. Chem. Soc.* **1970**, *92*, 3187.

[11] (a) Goossen, L. J.; Thiel, W. R.; Rodriguez, N.; Linder, C.; Melzer, B. *Adv. Synth. Catal*. **2007**, *349*, 2241; (b) Goossen, L. J.; Manjolinho, F.; Khan, B. A.; Rodriguez, N. *J. Org. Chem*. **2009**, *74*, 2620.

[12] Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc*. **2005**, *127*, 10323.

[13] Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Org. Lett*. **2007**, *9*, 2441.

[14] Nuñez Magro, A. A.; Eastham, G. R.; Cole-Hamilton, D. J. *Dalton Trans*. **2009**, 4683.

[15] (a) Nilsson, M. *Acta. Chem. Scand.* **1966**, *20*, 423; (b) Nilsson, M.; Ullenius, C. *Acta. Chem. Scand.* **1968**, *22*, 1998.

[16] (a) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem. Int. Ed*. **1997**, *36*, 155; (b) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem. Eur. J.* **2000**, *6*, 1147.

[17] (a) Goossen, L. J.; Deng, G.; Levy, L. M. *Science*, **2006**, *313*, 662; (b) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. *J. Am. Chem. Soc.* **2007**, *129*, 4824.

[18] Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 7103.

[19] Goossen, L J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248.

[20] Goossen, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem. Int. Ed.* **2010**. *49*, 1111.

[21] Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.

[22] Wang, Z.; Ding, Q.; He, X.; Wu, J. *Tetrahedron*, **2009**, *65*, 4635.

[23] Becht, J.-M.; Le Drian, C. *Org. Lett.* **2008**, *10*, 3161.

[24] Zhang, F.; Greaney, M. F. *Org. Lett*. **2010**, *12*, 4745.

[25] Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc*. **2006**, *128*, 11350.

[26] Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem*. **2010**, *75*, 1550.

[27] Shang, R.; Xu, Q.; Jiang, Y.-Y.; Wang, Y.; Liu. L. *Org. Lett.* **2010**, *12*, 1000.

[28] Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 9350.

[29] Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev*. **2011**, *40*, 2761.

[30] Dai, J.-J.; Liu, J.-H; Luo, D.-F.; Liu, L. *Chem. Commun.* **2011**, *47*, 677.

[31] Voutchokva, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312.

[32] Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194.

[33] Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc*. **2002**, *124*, 11250.

[34] Fu, Z.; Huang, S.; Su, W.; Hong, M. *Org. Lett.* **2010**, *12*, 4992.

[35] Sun, Z.-M.; Zhang, J.; Zhao, P. *Org. Lett.* **2010**, *12*, 992.

[36] Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2007**, *72*, 5362.

[37] Wang, C.; Rakshit, S.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 14006.

[38] Zhang, M.; Zhou, J.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Chem. Commun.* **2011**, *46*, 5455.

[39] Y. Luo, J. Wu, *Chem. Commun.* **2010**, *46*, 3785.

[40] Lindh, J.; Sjörberg, P. J.; Larhed, M. *Angew.Chem. Int. Ed.* **2010**, *49*, 7733.

[41] Sun, Z.-M.; Zhao, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 6726.

[42] (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174; (b) Ackermann, L.;Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792.

[43] Lafrance, M.; Rowly, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc*. **2006**, *128*, 8754.

[44] Daugulis, O.; Zaitsez, V. G. *Angew. Chem. Int. Ed*. **2005**, *44*, 4046.

[45] Yeung, C. S.; Dong, V. *Chem Rev*. **2011**, *111*,1215.

[46] Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

[47] Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc*. **2010**, *132*, 1822.

[48] Humphrey, G. R.; Kuethe, J. T. *Chem. Rev*. **2006**, *106*, 2875.

[49] Direct arylation of indoles can afford C2 or C3 adducts depending on the reaction conditions. For selected examples, see: (a) Lane, B. S.; Sames, D. *Org. Lett*. **2004**, *6*, 2897; (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050; (c) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc*. **2006**, *128*, 4972; (d) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926; (e) Stuart, D. R.; Fagnou, K. *Science*, **2007**, *316*, 1172; (f) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072; (g) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett*. **2008**, *49*, 4050; (h) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1473; (i) Joucla, L.; Batail, N.; Djackovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929. For reviews, see: Joucla, L.; Djackovitch, L. *Adv. Synth. Catal*. **2009**, *351*, 673.

[50] Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 8172.

[51] Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc*. **2008**, *130*, 2926.

[52] (a) Miller, W. T.; Sun, K. K.; *J. Am. Chem. Soc*. **1970**, *92*, 6985; (b) Furuya, T.; Strom A. E.; Ritter, T.; *J. Am. Chem. Soc.* **2009**, *131*, 1662; (c) Furuya T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860.

[53] Greenwood, N. N.; Earnshaw, A. **1984**, *Chemistry of the Elements*. New York: Permagon Press. pp. 1185–87.

[54] Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem. Eur. J.* **2010**, *16*, 5876.

[55] Zhang, F.; Greaney, M. F.; *Angew. Chem. Int. Ed*. **2010**, *49*, 2768.

[56] Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo. C.-C. *Org. Lett*. **2010**, *12*, 1564.

[57] Zhao, H.; Wei, Y.; Xu, J.; Kan, J.; Su, W.; Hong, M. *J. Org. Chem*. **2011**, *76*, 882.

[58] (a) Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem. Int. Ed*. **2009**, *48*, 792; (b) Li, Z.; Li, C.-J. *J. Am. Chem. Soc*. **2005**, *127*, 6968.

[59] (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510; (b) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 17676.

[60] Ueura, K.; Satoh, T.; Miura, M. *Org. Lett*. **2007**, *9*, 1407.

[61] (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem*. **1998**, *63*, 5211.

[62] Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097.

[63] (a) Zhang, Y.-H.; Yu. J.-Q. *J. Am. Chem. Soc*. **2009**, *131*, 14654; (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082

[64] Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem. Int. Ed*. **2008**, *47*, 5215

[65] For Hg(II)-mediated decarboxylation see: Gilman, H.; Wright, G. F. *J. Am. Chem. Soc*. **1933**, *55*, 3302.

[66] Miller, T. M.; Sun, K. K. *J. Am. Chem. Soc.* **1970**, *92*, 6985.

[67] Xue, L.; Su, W.; Lin, S. *Dalton Trans*. **2011**, *40*, 11926.

[68] Goossen, L. J.; Linder, C.; Rodriguez, N.; Lange, P. P.; Fromm, A. *Chem. Commun*. **2009**, 7173.

[69] Goossen, L. J.; Lange, P. P.; Rodriguez, N.; Linder, C. *Chem. Eur. J.* **2010**, *16*, 3906.

[70] (a) Noyori, R. *Chem. Soc. Rev*. **1989**, *18*, 187; (b) Pu, L. Chem. Rev. **1998**, *98*, 2405.

[71] (a) Nielsen, M. B.; Driedrich, F. *Chem. Rev*. **2005**, *44*, 2482; (b) McCulloch, I.; Heeney, M.; Chabinyc, M. L.; DeLongchamp, D.; Kline, R. J.; Cölle, M.; Duffy, W.; Fischer, D.; Gundlach, D.; Hamadani, B.; Hamilton, R.; Richter, L.; Salleo, A.; Shkunov, M.; Sparrowe, D.; Tierney, S.; Zhang, W. *Adv. Mat*. **2009**, *21*, 1091.

[72] (a) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev*. **2001**, *30*, 145; (b) Vrettu, M.; Gray, A. A.; Brewer, A. R. E.; Barrett, A. G. M.; *Tetrahedron* **2007**, *63*, 1487.

[73] (a) Nicolau, K. C.; Boddy, C. N. C.; Bräse, S. Winssinger, N. *Angew. Chem. Int. Ed*. **1999**, *38*, 2096; (b) Baudoin, O.; Cesario, M.; Guenard, D.; Gueritte, F. *J. Org. Chem*. **2002**, *67*, 1199.

[74] For selected examples on homocoupling of haloarenes see: (a) de França, K. W. R.; Oliveira, J. L.; Florencio, T.; da Silva, A. P.; Navarro, M.; Leonel, E.; Nedelec, J.-Y. *J. Org. Chem*. **2005**, *70*, 10778; (b) Cahiez, G.; Chaboche, C.; Mahuteau-Betzer, F.; Ahr, M. *Org. Lett.* **2005**, *7*, 1943; (c) Qi, C.; Sun, X.; Lu, C.; Yang, J.; Du, Y.; Wu, H.; Zhang, X.-M. *J. Organomet. Chem.* **2009**, *694*, 2912; (d) Zeng, M.; Du, Y.; Shao, L.; Qi, C. Zhang, X.-M. *J. Org. Chem*. **2010**, *75*, 2556; (e) Nadri, S.; Azadi, E.; Ataei, A.; Joshaghani, M.; Rafiee, E. *J. Organomet. Chem*. **2011**, *696*, 2966; (f) Peng, J.; Liu, X.; Kishi, Y. *Tet. Lett*. **2011**, *52*, 2172.

[75] For selected examples on homocoupling of organometallic compounds see: (a) Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788; (b) Sakurai, H.; Tsunoyama, H.; Tsukuda, T. *J. Organomet. Chem.* **2007**, *692*, 368; (c) Maji, M. S.; Pfeifer, T.; Studer, A. *Angew. Chem. Int. Ed*. **2008**, *47*, 9547 (d) Matsuda, T.; Asai, T.; Shiose, S.; Kato, K. *Tet. Lett*. **2011**, *52*, 4779; (e) Cheng, G.; Luo, M. *Eur. J. Org. Chem*. **2011**, 2519.

[76] (a) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074; (b) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10830; (c) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc*. **2007**, *129*, 13927; (d) Rong, Y.; Li, R.; Lu, W. *Organometallics*, **2007**, *26*, 4376; (e) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M. Tse, M. K. *Chem. Commun*. **2008**, 386; (f) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc*. **2009**, *131*, 17052; (g) Oi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2008**, *10*, 1823; (h) Li, Y.; Wang, W.-H.; Yang, S.-D.; Li, B.-J.; Fengab, C.; Shi, Z.-J. *Chem Commun*, **2010**, 4553 (i) Li, Z.; Wang, Y.; Huang, Y.; Tang, C.; Xu, J.; Wu, X. Yao, H. *Tetrahedron* **2011**, *67*, 5550; (j) Li, X.-L.; Huang, J.-H.; Yang, L.-M. *Org. Lett*. **2011**, *13*, 4950.

[77] Xie, K.; Wang, S.; Yang, Z.; Liu, J.; Wang, A.; Li, X.; Tan, Z.; Guo, C.-C.; Deng, W. *Eur. J. Org. Chem.* **2011**, 5787,

[78] Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

[79] Phipps, R. J.; Gaunt, M. J. *Science*, **2009**, *323*, 1593.

[80] Duong, H. A.; Gilligan, R. E., Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed*. **2011**, *50*, 463.

[81] Ciana, C.-L.; Phipps, R. J.; Brandt, J. R.; Meyer, F.-M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 458.

[82] Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.

[83] Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed*. **2009**, *48*, 6511.

[84] Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc*. **2007**, *129*, 9879.

[85] Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc*. **2009**, *131*, 11234.

[86] Vicente, J.; Arcas, A.; Julia-Hernandez, F.; Bautista, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 6896.

[87] (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302; (b) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc*. **2009**, *131*, 17050; (c) Powers, D. C. Benitez, D.; Tkatchouk, E.; Goddard III, W. A. Ritter, T. *J. Am. Chem. Soc*. **2010**, *132*, 14092.

[88] (a) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 5776; (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2011**, *76*, 3024.

[89] Lu, P.; Boorman, T.; Slawin, A.M. Z.; Larrosa, I. *J. Am. Chem. Soc*. **2010**, *132*, 5580.

[90] Fackler, J. P.; Khan, M. N. I.; King, C.; Staples, R. J.; Winpenny, R. E. P. *Organometallics*, **1991**, *10*, 2178.

[91] (a) Lauterbach, T.; Livendhal, M.; Rosellon, A.; Espinet, P.; Echavarren, A. M. *Org. Lett*. **2010**, *12*, 3006; (b) Buchwald, S. L.; Bolm, C. *Angew. Chem. Int. Ed*. **2009**, *48*, 5586.

[92] Grodzicki, A.; Lakomska, I.; Piszczek, P.; Szymanska, I.; Szlyk, E. *Coord. Chem. Rev.* **2005**, *249*, 2232.

[93] (a) Hashmi, A. S. K.; Lothschutz, C.; Dopp, R.; Rudolph, M.; Ramamurthu, T. D.; Rominger, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 8243; (b) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022; (c) Shi, Y.; Ramgren, S. D.; Blum, S. A. *Organometallics* **2009**, *28*, 1275.

[94] (a) Janz, K.; Kaila, N. *J. Org. Chem*. **2009**, *74*, 8874; (b) Chowdhury, S.; Roy, S. *J. Org. Chem*. **1997**, *62*, 199.

[95] Dupuy, S.; Lazreg, F.; Slawin, A. M. Z.; Cazin, S. J.; Nolan, S. P. *Chem. Commun*. **2011**, *47*, 5455.

[96] Johnson, M. T.; van Rensburg, J. M. J.; Axelsson, M.; Ahlquist, M. S. G.; Wendt, O. F. *Chem. Sci*, **2011**, *2*, 2373.

[97] (a) Würtz, S.; Glorius, F. *Acc. Chem. Res*. **2008**, *41*, 1523; (b) Fortman, G.; Nola, S. P. *Chem. Soc. Rev*. **2011**, *40*, 5151.

[98] Stahl, S. S. *Angew. Chem. Int. Ed*. **2004**, *43*, 3400.

[99] Murphy, J. M.; Liao, X.; Hartwig. J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.

[100] Liegault, B.; Lee, D.; Huestic, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem*. **2008**, *73*, 5022.

[101] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc*. **2008**, *129*, 12072.

[102] Avendano, C.; Sanchez, J. D.; Menendez, J. C. *Synlett*, **2005**, *1*, 107.

[103] G. Cahiez, C. Chaboche, F. Mahuteau-Betzer and M. Ahr, *Org. Lett.*, **2005**, *7*, 1943.

[104] Bjørsvik, H. R.; Rodríguez, R.; Liguori, L. *J. Org. Chem.*, **2004**, *69*, 7720.

[105] B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, *J. Am. Chem. Soc*. **2008**, *130*, 14468.

[106] C. Wolf, K. Ekoue-Kovi, *Eur. J. Org. Chem.* **2006**, *8*, 1917.

[107] Fleckenstien, C. A.; Plenio, H. *Chem. Eur. J*. **2007**, *13*, 2701.

[108] L. J. Goossen, N. Rodriguez, C. Linder, *J. Am. Chem. Soc.* **2008**, *130*, 15248.

[109] R. Shang, Q. Xu, Y.-Y. Jiang, Y. Wang, L. Liu, *Org. Lett.* **2010**, *12*, 1000.

[110] (a) A. M. Roe, R. A. Burton, G. L. Willey, M. W. Baines, A. C. Rasmusen, *J. Med. Chem.* **1968**, *11*, 814; (b) V. Padelidakis, W. Tyra, D. Naumann, *J. Fluorine. Chem.* **1999**, *99*, 9.